THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—18TH YEAR. SYDNEY, SATURDAY, JULY 11, 1931. No. 2.

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The Mathison Lectures.[1]

LECTURE II.

THE IMMUNITY OF AUSTRALIAN SNAKES TO THEIR OWN VENOMS.

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THE astonishing immunity of venomous serpents to their own venoms has long been recognized—in fact, since Fontana,[1] late in the eighteenth century, first observed that a species of European viper and an innocuous grass snake were both immune to the venom of the viper. Fontana and a number of workers who succeeded him in the first half of the nineteenth century, regarded the immunity of venomous snakes as absolute, but in the latter half of the nineteenth century the experiments of Claude Bernard,[2] Weir Mitchell,[3] Fayrer[4] and of Waddel[5] showed that death, usually delayed, might follow the bite of a venomous snake or the injection of a sufficient amount of liquid venom.

The immunity of snakes to snake venom was placed on a quantitative basis by the experiments of C. Phisalix,[6] who injected weighed doses of dried viper venom into *Vipera aspis* and showed that this species, though highly immune, was not absolutely insusceptible to the effects of its own venom. When the venom was injected intraperitoneally, symptoms were produced when the dose exceeded 40 milligrammes. A dose of 45 milligrammes caused striking loss of sensation and paralysis lasting several days. To cause death, which took place in from twenty

[1] These experiments were carried out under a grant from the Commonwealth Department of Health.

to thirty hours, doses of the order of 100 to 120 milligrammes (five times the venom yield of this reptile) were necessary. If, however, the venom were injected intradurally through the occipito-atlantal membrane, two to four milligrammes caused rapid death. In view of the extreme unlikelihood of injection by natural bite in this region or into the brain through the tough plates covering the dorsal surface of the head and the bones of the cranium, he restated Fontana's dictum concerning the immunity of the viper. "Under the conditions of natural inoculation the venom of the viper is not a poison for its own species."

The Australian venomous snakes possess an extremely high degree of immunity both to their own venoms and to those of closely allied species. In Tables I and II are set out a few results of the subcutaneous injection of various venoms into tiger snakes (*Notechis scutatus*) and death adders (*Acanthophis antarcticus*) which indicate the degree of immunity in these two species. These results are closely paralleled by those of similar experiments upon the copper-head (*Denisonia superba*) and the black snake (*Pseudechis porphyriacus*). A less striking degree of resistance is exhibited by non-venomous snakes as is shown by the results of experiments summarized in Table III on the carpet snake (*Python spilotes* var. *varigatus*).

The lethal action of the Australian venoms when injected subcutaneously in all these snakes is similar to their action in mammalian species, the powerful neurotoxins causing paralysis of the musculature and failure of respiration. The venomous snakes also tolerate without symptoms the intravenous or intraarterial injection of large doses of dry venom, a tiger snake or copper-head of 150 grammes weight exhibiting no symptoms following the injection of 20 or 30 milligrammes of dry venom dissolved in a suitable volume of saline solution. Larger doses cause failure of respiration and paralysis of movement, commencing at the head end and spreading distally.

The extent of the immunity displayed by the Australian snakes, notably by the venomous species, is the more remarkable when it is realized how potent the neurotoxic venoms are in their action upon mammals. In Table IV are set out the approximately lethal doses of some of these venoms in milligrammes per kilogram of body weight for a number of experimental animals.

It will be observed that there is a by no means inconsiderable range of variation observed in the natural immunity of various animals to venom. The cat, for example, is about five times and the rat about twenty times as resistant as the guinea-pig to the venom of the tiger snake. The immunity of the venomous snakes is, however, so striking (many thousand times that of the guinea-pig) as to raise the question as to whether it does not differ from that of other animals in kind as well as in degree.

In the present lecture I propose to discuss two problems concerning the high immunity of the Aus-

TABLE I.

The Effect of the Subcutaneous Injection of Various Venoms in the Tiger Snake (Notechis scutatus).

Venom.	Weight in Grammes.	Dose in Milligrammes.	Approximate Dose in Milligrammes per 100 Grammes.	Result.
Notechis scutatus (tiger snake)	130	178	137	Sick for three days; recovered.
	206	134	65	No symptoms.
Pseudechis porphyriacus (black snake)	140	93	66	Died on the sixth day.
Denisonia superba (copper-head)	180	191	106	Died on the third day.
	122	95	78	Paresis from second to fifth day; recovered.
	140	95	68	Paresis from second to seventh day; recovered.
Acanthophis antarcticus (death adder)	110	141	128	Died on the eighth day.
	120	94	78	No symptoms.
	174	94	54	Slight symptoms; recovery.
Naia naia (cobra)	146	92	63	Died in 1 hour.
	180	46	26	Died in 1 hour 20 minutes.
	166	18·3	11	Died in less than 17 hours.
	105	6·3	6	Died in less than 20 hours.
	160	9·2	5·7	Died in less than 20 hours.
	125	6·4	5·1	Sick for several days; survived.
	196	7·45	3·8	No symptoms; survived.
	125	4·6	3·7	Died in less than 20 hours.
	134	4·6	3·4	Died in 24 hours.
	140	4·6	3·3	Died in 24 hours.
	120	2·3	1·9	Died in 24 hours.
	135	2·3	1·7	No definite symptoms; survived.
	130	2·3	1·8	Sick for 4 days; survived.
	170	1·8	1·06	Sick for 2 days; survived.
Vipera russelli (Daboia)	120	95	79	Died on the fifth day.
	125	47·5	38	No definite symptoms.

TABLE II.

The Effect of the Subcutaneous Injection of Various Venoms in the Death Adder (Acanthophis antarcticus).

Venom.	Weight in Grammes.	Dose in Milligrammes.	Approximate Dose in Milligrammes per 100 Grammes.	Result.
Acanthophis antarcticus (death adder).. ..	49	188	384	Died in less than 47 hours.
	30	94	313	Died on the third day.
	64	60·2	94	Died in 10¼ hours.
	255	179	70	Survived without symptoms.
	110	37·4	34	Survived without symptoms.
Notechis scutatus (tiger snake)	42	89	212	Died in less than 47 hours.
	34	44·5	131	Died on the third day.
	245	110	45	Died on the third day.
	160	58	36	Survived without symptoms.
Denisonia superba (copper-head)	44	95	216	Died in less than 47 hours.
	32	48	150	Died in 21 hours.
	120	86	72	Died on the ninth day.
	280	134	48	Died on the eighth day.
	140	53·5	38	Survived without symptoms.
Pseudechis porphyriacus (black snake).. ..	42	93	221	Died in less than 47 hours.
	73	68	93	Died in 28 hours.
	110	77	70	Died on the second day.
	225	104	46	Survived without symptoms.
Naia naia (cobra)	39	4·7	12	Died on the second day.

tralian venomous snakes: (i) Is there any reasonable explanation of the acquirement by these species of the elapine family of so high a degree of immunity? (ii) Upon what does this natural immunity depend? It may first be well to clear the ground by excluding the obvious possibility that the immunity of the reptiles is wholly dependent upon their being "cold blooded."

IS THE IMMUNITY OF SNAKES DUE TO THE FACT THAT THEY ARE "COLD BLOODED."

Although, generally speaking, "cold blooded" species are more resistant to the action of venoms than "warm blooded" animals, and it must be admitted therefore that a generally low body temperature and consequent slow metabolism may account in part for the resistance of the former, much evidence has been accumulated which effectively disposes of the view that the high resistance of venomous snakes is wholly dependent upon this factor.

In the first place, there are very wide variations in the resistance of cold blooded animals to venom. This was shown on a large scale by Noguchi,[7] who studied the effects of the venoms of the cobra, of a rattle snake and of the water moccasin in some species of *Reptilia, Amphibia, Pisces, Insecta, Crustacea, Vermes, Mollusca* and *Echinodermata.*

In the second place it is well established that the resistance of some hibernating mammals is con-

TABLE III.

The Effect of the Injection of Various Venoms on the Carpet Snake (Python spilotes var. *variegatus).*

Venom.	Weight in Grammes.	Dose in Milligrammes.	Approximate Dose in Milligrammes per 100 Grammes.	Result.
Acanthophis antarcticus (death adder).. ..	700	197	28	Died on the fourth day.
	790	47·4	6	No symptoms.
Notechis scutatus (tiger snake)	331	89	27	Died in less than 47 hours.
	470	80	17	Moderate symptoms; recovery by fifth day.
	530	44·5	8·4	No symptoms.
Denisonia superba (copper-head)	454	191	42	Died on the third day.
	420	96	23	Died on fifth day.
Pseudechis porphyriacus (black snake).. ..	580	96	16·6	No symptoms.
Naia naia (cobra)	440	18·4	4·2	Moderate symptoms; recovered on the fifth day.

TABLE IV.

Subcutaneous Certainly Lethal Doses of the Venoms of Some Common Australian Snakes compared with those of the Cobra. Doses in Milligrammes per Kilogram of Body Weight.

Species Tested.	*Acanthophis antarcticus.*	*Notechis scutatus.*	*Denisonia superba.*	*Pseudechis porphyriacus.*	*Naia naia.*
Horse	About 0·04	About 0·005	About 0·02	—	—
Sheep	0·025 (Fairley)	0·01 (Fairley)	0·1 (Fairley)	About 0·8 (Fairley)	—
Goat	—	About 0·018 (Fairley)	—	—	—
Monkey	About 0·15	About 0·02	—	0·5–0·8	About 1·3 (Acton & Knowles)
Cat	About 0·5	About 0·1	About 1·2	7·0–10·0	—
Rabbit	0·15	0·045	0·7 (for large rabbits, 0·5)	More than 2	—
Guinea-pig	0·15	0·02	0·06	1·2–1·6	0·5 (Noguchi)
Rat	0·4	More than 0·4	1·4	2·0	0·6 (Noguchi)
Mouse	0·7	More than 0·25	1·2	3·5	—
Carpet snake (*Python spilotes*) ..	More than 60	More than 170	About 230	More than 166	More than 45
Tiger snake (*Notechis scutatus*) ..	More than 780	More than 1,370	More than 780	—	About 60
Copper-head (*Denisonia superba*) ..	More than 500	More than 930	More than 444	—	About 50
Death adder (*Acanthophis antarcticus*)	More than 700	More than 360	More than 380	More than 460	—

siderably greater than that of many cold blooded species. For example, Marie Phisalix[8] has summarized the minimal lethal doses of the venom of *Vipera aspis* given subcutaneously or intraperitoneally to a large number of species. Though the viper and grass snake have by far the greatest natural immunity among the species studied, the dormouse is nearly three times as resistant as the frog, and the hedgehog has about three times the resistance of the toad and nearly four times that of the crocodile. It is of interest also that the white mouse with a very high body temperature has the same minimum lethal dose as the toad. It is evident, then, that the wide range of variation in natural immunity to snake venom met with in the cold blooded animals overlaps with those variations observed among warm blooded animals.

Thirdly, a comparison of the degree of immunity of the Australian venomous snakes to closely allied venoms from Australian snakes with their immunity to the venom of the cobra (Table I) makes it evident once and for all that "cold bloodedness" cannot be the decisive factor in determining the high immunity of the Australian elapines to their own and allied venoms.

To indicate the general toxicity of the venoms I have expressed the resistance of the tiger snake in numbers of certainly lethal doses (in milligrammes per 100 grammes) of the various venoms for the guinea-pig. For this last mentioned animal the certainly lethal dose of tiger snake venom is 0·002 milligramme; of copper-head venom, 0·007; of death adder venom, 0·015; of black snake venom, 0·15; and of cobra venom about 0·05 milligramme per 100 grammes. A tiger snake weighing 100 grammes can withstand about 70,000 guinea-pig lethal doses of tiger snake venom, 13,000 of copper-head venom, 5,000 of death adder venom, less than 500 of black snake venom, and less than 100 guinea-pig lethal doses of the venom of the cobra.

The resistance exhibited to these last two venoms is only of a moderate order. This is probably dependent in part upon the presence in both of powerful hæmotoxic elements, but the possibility that geographical considerations may determine the relatively low immunity of Australian snakes to the venom of a foreign snake of the same family cannot be disregarded.

How has the "Natural" Immunity of Venomous Snakes been Attained?

The immunity of snakes to their own venoms would inevitably result if venom or its constituents were intermittently or constantly present in the circulating blood, only those individuals which possessed a protective mechanism being capable of surviving or of propagating their species. There are at least three possibilities in this regard.

The first method by which venom might gain access to the blood stream was suggested by Waddel,[5] who thought that it might be absorbed from abrasions of the mucosa of the alimentary tract. Snakes normally swallow a good deal of venom in and with their prey and probably at other times as well. There is no evidence concerning the frequency of abrasions, but intestinal worms are common and more than once we have found them lying in a channel in the mucosa. They must frequently cause lesions from which venom could be absorbed.

Waddel's view has been dismissed by Marie Phisalix, who has admirably reviewed the earlier work on this problem, on the ground that venom is destroyed in the alimentary tract. This statement appears to rest upon Fraser's experiments on the neutralizing action of the bile, which, in the case of the Australian snakes, is very slight.

The Neutralizing Action of the Bile of Serpents.

Fraser[9] first drew attention to the activity of bile, particularly that of venomous serpents, in neutralizing snake venom.

The neutralizing agent was in the alcohol insoluble fraction of the bile and was associated with the proteins and pigments and not with the bile salts, cholesterin, lecithin and other constituents which are soluble in alcohol. The degree of protection which Fraser observed is indicated by his later experiments (1898) with the venom of the Indian

cobra (*Naia naia*). This venom in a dose of 0·25 milligramme per kilogram (a dose just greater than the minimal lethal dose for the rabbit) was mixed with varying quantities of dried bile dissolved in a few tenths of a cubic centimetre of water and allowed to remain in contact for ten minutes before injection. The amounts of dry bile from various venomous snakes in milligrammes per kilogram which sufficed under these conditions to reduce the dose to a sublethal one, ranged from 0·5 to 4 milligrammes. The degree of protection afforded in these experiments is really not so striking as appears, since the destruction or neutralization of half, a third, or even less of the venom would suffice to make the dose sublethal. The actual amount of venom neutralized by the amounts of bile given in Fraser's experiments is probably on a liberal estimate about 0·1 milligramme of cobra venom. In the case of the Australian snakes the neutralizing or destructive action of bile is trivial, even when the bile is allowed to remain in contact with the venom for several hours at room temperature.

Fresh bile was collected aseptically from tiger snakes. Their gall bladders were excised and punctured and the bile was allowed to flow into sterile test tubes. Experiments were made both with fresh bile and with pooled dry bile. The experiments were carried out upon guinea-pigs of about 200 grammes weight. These were occasionally killed by doses of 0·1 cubic centimetre of fresh bile (equivalent to 7–8 milligrammes of dry bile) which, injected subcutaneously, produced an intense local reaction. Using a sample of pooled fresh bile, which was not lethal in this dosage when diluted one in ten with saline solution, we found that mixtures containing 0·05–0·1 cubic centimetre of bile with 0·005 milligramme of tiger snake venom (a little more than a single lethal dose) which were allowed to stand for seven and a half hours at 20° C. invariably caused death when injected into guinea-pigs. Since Fraser's experiments were made with weighed dry bile and in order to make it certain that dilution of the bile was not responsible for its inactivity, dried bile was used in a few experiments. In one such, for example, 5 milligrammes of dried pooled tiger snake bile dissolved in 0·5 cubic centimetre of saline solution was found to cause only a local lesion in guinea-pigs of 200 grammes weight. This amount of dry bile was mixed with 0·005 milligramme of tiger snake venom in 0·5 cubic centimetre of saline solution and allowed to stand for five hours at 20° C. Guinea-pigs injected with this mixture died regularly on the second day.

It is clear, therefore, that the neutralizing action of the bile of the Australian snakes is too small to be of any importance.

Is Venom Entirely Destroyed in the Alimentary Tract of the Snake?

Before administering venom orally and endeavouring to ascertain whether it could be detected in the excreta of snakes, it was of importance to ascertain the probable time occupied in passage through the alimentary canal. Two different kinds of experiment were made to elucidate this point.

With the cooperation of Dr. Barbara Wood a barium meal was administered to a tiger snake in which for convenience the venom glands had been removed. This snake had fed on a mouse four days earlier and in the first film the remains of this meal were clearly visible low down in the intestine. The meal, two cubic centimetres of a thick suspension of barium sulphate, was administered into the pharynx with a Bashford tumour syringe. The first film was taken fifteen minutes later, the next after the lapse of six hours. Films were taken at 24 hours, 30 hours, 48 hours and 72 hours. After 48 hours some of the barium was near the vent, but most of it was held up at the remains of the last meal and was passed with these on the sixth day. (Normally after ingesting a meal the undigested residue is excreted on about the fifth day or later.)

At the same time another snake which had an empty alimentary tract was given two cubic centimetres of Higgin's waterproof Indian ink. This was administered into the pharynx. The excreta expressed after twenty-four hours were free from ink, but a good deal was obtained in the sample of excreta expressed after forty-eight hours.

With these results before us we administered venom orally in several snakes, collecting samples of excreta daily by gentle digital expression. These were accurately diluted one in ten with sterile saline solution and filtered through a Seitz filter. The filtrates, which were free from microorganisms and *débris*, were tested for the presence of venom by injection into guinea-pigs.

A fasting copper-head, captured 12 days earlier and weighing 100 grammes, was given 100 milligrammes of tiger snake venom by injection into the pharynx after expressing the contents of the lower part of the intestine and cloaca. Further samples of excreta were taken one, two, three, four and five days after the venom had been given. The excreta obtained before the administration of venom and those procured at the end of the first, second, third and fifth days, diluted one in ten and filtered were non-toxic in a dose of 1·0 cubic centimetre (equivalent to 0·1 cubic centimetre of excreta). The filtered and diluted sample obtained at the end of the fourth day was highly toxic. Doses of 0·1 and 0·05 cubic centimetre of the one in ten dilution killed guinea-pigs of 250 grammes weight in half an hour and 0·1 cubic centimetres of a one in one hundred dilution killed in a few hours. A dose of 0·05 cubic centimetre of this last dilution caused no symptoms.

The volume of this last sample of excreta was 0·6 cubic centimetre and, assuming that its toxicity was due to the venom, a reasonable assumption in view of the fact that the filtered excreta of fasting snakes are invariably non toxic in doses of the order of 0·1 cubic centimetre (1·0 cubic centimetre of 1:10 filtrate, one-thirtieth of the venom had escaped the destructive or absorptive functions of the intestinal mucosa during the time occupied by its passage through the alimentary tract—four days. In this time the destruction caused by bacterial action alone must have been by no means inconsiderable.

It may be urged that in experiments of this type the probability of excretion through the urinary tract should be considered. There are several reasons why the increased toxicity of the excreta cannot be so explained. First, as will shortly be seen, there is no evidence that under these circumstances any appreciable quantity of venom gains entry into the circulating blood. Secondly, when venom has actually been injected into the blood stream, if it be excreted in this way, the process must be an exceedingly slow one, since we have not been able to detect it following the injection of large doses intravenously. Finally, the appearance of toxicity in the excreta, in this case on the fourth day only, is in accord with the passage of some venom through the alimentary tract rather than with a sudden excretion through the Wolffian ducts.

Though these results remove any *a priori* objections to Waddel's hypothesis, we have subjected it to direct test by experiment. Before proceeding further it is necessary to detail briefly certain facts of which more will be said at a later stage. The plasma of snakes is toxic, but this toxicity may be removed by heating to 58° C. for half an hour and the heated plasma is then found to be antitoxic. Now if venom be added to plasma and the mixture be heated, a certain amount of the venom will be neutralized by the plasma and a certain small amount of the added toxicity will be destroyed by

the subsequent heating. If, therefore, venom gain entry to the circulating blood, examination of heated samples of plasma should display its presence either by diminution of the neutralizing power of the heated plasma (if only small amounts of venom have gained access) or by the acquirement of toxicity (if larger amounts have entered the circulation).

Using these well established facts, we attempted to ascertain whether, when venom was introduced orally, there was any consequent change in the toxicity or in the neutralizing power of heated plasma. A number of experiments of this kind were performed and in no case were we able to obtain evidence of the absorption of venom into the blood stream. As an example the following experiment may be quoted.

A tiger snake weighing 180 grammes captured on the previous day (when it had bitten itself and been bitten by other tiger snakes which were in the bag with it) was anæsthetized with ether. The inferior *vena cava* was exposed and a preliminary sample of 1·0 cubic centimetre of blood was taken from it. A dose of 100 milligrammes of tiger snake venom in two cubic centimetres of saline solution was now introduced into the œsophagus. Samples of blood were taken from the inferior *vena cava* fifty minutes, two hours, three and a quarter hours, eight hours and twenty-four hours later. At this last time, a sample of excreta (the first since the experiment started) was collected from the snake. Of this 0·1 cubic centimetre (diluted one in ten and filtered) injected subcutaneously into a guinea-pig of 200 grammes (certainly lethal dose of tiger venom 0·004 milligramme) caused no symptoms. No appreciable quantity of venom had therefore passed through the alimentary tract or been excreted in the urine during this period. The samples of blood, after dilution with an equal volume of 1% citrate saline solution, were centrifuged and the plasma was heated to 58° C. for half an hour. The death times of guinea-pigs of 200 grammes injected subcutaneously in the abdominal wall with 1·0 cubic centimetre and 0·5 cubic centimetre of the citrated plasmas (equivalent to 0·5 and 0·25 cubic centimetre of snake plasma) are set out in Table V.

TABLE V.

Results of the Injection of Samples of Plasma from a Snake which had received orally 100 Milligrammes of Tiger Snake Venom.

Time.	Dose of Plasma in Cubic Centimetres.	Death Times.
Before administration of venom	0·5	Less than 40 hours.
	0·25	Less than 64 hours.
50 minutes after administration	0·5	Less than 66 hours.
	0·25	Less than 88 hours.
2 hours after administration ..	0·5	Less than 66 hours.
	0·25	90 hours.
3½ hours after administration ..	0·5	Less than 66 hours.
	0·25	94 hours.
8 hours after administration ..	0·5	Less than 90 hours.
24 hours after administration ..	0·5	Survived without symptoms.

Owing to the recent addition of tiger snake venom to the plasma through the bites which the reptile had received, any small addition of venom by absorption from the alimentary canal should have increased the toxicity of the plasma, since its neutralizing power was already fully taken up. On the contrary, the lengthening of the death times shows a slight diminution of toxicity of the plasma during the experiment, though this may possibly be related to dilution of the plasma from loss of blood by sampling.

In several other experiments upon snakes, which had been isolated for some days and in which the heated plasma was not toxic in doses of 1·0 to 4·0 cubic centimetres, no evidence of any absorption of venom could be obtained by the method shown or by titrating the heated samples for their protective power.

Though the *a priori* grounds of objection have been disposed of, our results are on the whole unfavourable to Waddel's hypothesis, though they do not exclude the possibility of absorption of venom in a non-toxic form. This, even if it could be shown to occur, could hardly be regarded as an effective stimulus for the development of species immunity.

The second possibility in regard to the development of immunity has been explored by Phisalix and Bertrand, who put forward the view that the venom glands secrete into the blood stream a toxic internal secretion identical with venom or at least with some of its constituents.

The researches of Leydig,[10] Phisalix and Bertrand,[11] Jourdain[12] and Alcock and Rogers[13] have shown that the essential difference between venomous and non-venomous snakes lies in the possession by the latter of an apparatus for the inoculation of venom, since the parotid gland of non-venomous snakes furnishes a toxic secretion. Furthermore, the serum of non-venomous snakes (like that of the venomous species) is toxic when administered parenterally to animals. Phisalix and Bertrand[14] stressed the similarity of the effects produced in experimental animals by the serum of the viper and by its venom. They demonstrated[15] that by heating to 58° C. for half an hour the toxicity of viper serum was removed and a protective action against venom was unmasked. Finally, they showed[16] that the removal of the venom glands in vipers resulted after an interval of 67 days in a loss of the toxicity of the serum.

Calmette,[17] however, maintains that the toxic substances in the sera of venomous snakes, though similar in action, are not identical with venom, since they are heat labile. He suggests that the blood of venomous snakes contains diastatic substances of cellular origin which represent certain of the constituent elements of venom. He found that by repeatedly injecting non-lethal doses of cobra serum it was possible to immunize rabbits and guinea-pigs against several lethal doses of cobra venom. Stephens[18] and later Noc[19] showed that Calmette's antivenine could neutralize the lytic element in cobra serum, and Flexner and Noguchi[20] found that antisera prepared against the sera of certain North American snakes neutralized the lytic action of the homologous venoms.

There are, however, a number of considerations which weaken this evidence and make it uncertain whether the view of Phisalix and Bertrand or that

of Calmette can be regarded as offering a completely satisfactory explanation of the development of natural immunity in the venomous snakes.

In the first place, there are a large number of sera other than those of the ophidians which are toxic, and in not a few of these a protective action against at least some snake venoms can be unmasked by heat. Phisalix and Bertrand[21][22] have themselves investigated some of these. The local toxic and hæmolytic action of eel serum can be destroyed by heat and a protective action against viper venom can be demonstrated if an interval of twenty-four hours is allowed to elapse between the injection of the heated serum and that of the venom. The serum of the hedgehog, which eagerly seeks vipers for food and which is highly resistant to their bite, contains heat labile toxic and heat stable protective substances. Billard[23] has demonstrated the protective action of the serum of the dormouse, which is itself highly resistant to viper venom, and Calmette has shown that the serum of the mongoose has a neutralizing action on cobra venom, though not sufficient to account wholly for its immunity. It is important to note that in these last examples immunity appears to be a natural development to insure survival in an environment in which contact with venomous reptiles is inevitable, and that this response is to the menace of accidental bites. Why should not both venomous and non-venomous snakes themselves develop immunity in a similar manner?

In the second place, if bites by their fellows are as common generally among venomous reptiles in captivity as they are in Australia, all the evidence presented in regard to the presence in serum of toxic substances identical with venom is rendered suspect, unless reptiles to be used for experiment are isolated for some days previously, and the observations of Phisalix and Bertrand on the loss of toxicity of the serum after removal of the venom glands may be capable of a simpler explanation than the hypothesis of a toxic internal secretion by the glands. Further evidence seems necessary to show that the toxicity of the sera of venomous snakes is indeed due to the presence of either venom or provenin. The local effects which follow the subcutaneous injection of snake sera are very striking —congestion, hæmorrhage, œdema and even necrosis resulting. These effects are very well displayed following the injection of the sera of the Australian elapine snakes, but they resemble much more closely the effects produced by the injection of a viperine venom than those following the injection of the predominantly neurotoxic group of Australian venoms, and we have never observed after the injection of lethal doses of the fresh serum of Australian snakes into laboratory animals any clear evidence of the typical neurotoxic symptoms which occur following the subcutaneous injection of the corresponding venoms.

Though Kaufmann[24] has demonstrated that the intravenous injection of viper serum causes a profound fall of blood pressure like that caused by viper venom, this cannot be regarded as unassailable evidence of the presence of viper venom in the serum and but little stress can be laid on the finding by Phisalix and Bertrand[14] that the toxic substances in venom and serum were both precipitated by alcohol.

As far as the Australian snakes are concerned, there can be no question that their immunity is to neurotoxin and that death, when it occurs following the exhibition of enormous doses of venom, is caused by paralysis of all the musculature and finally of respiration. The criteria which must be demanded for the identification of venom in the plasma of the Australian reptiles are:

1. The demonstration of a neurotoxic constituent in the plasma which in the case of the serum of the tiger snake and copper-head should cause death with paralysis of the skeletal muscles and failure of respiration, and in that of the death adder (*Acanthopis antarcticus*) should be capable of producing like the venom a peripheral curara action on the skeletal muscle of *Lymnodynastes dorsalis*.

2. The toxic action of snake sera in animals should be completely masked by univalent antivenine prepared against the homologous venom.

3. Repeated injection of sera should afford protection against the neurotoxic action of the homologous venom.

4. The sera of rabbits immunized with snake sera to a high titre should give positive serological reactions with the homologous venom.

5. The sera of rabbits immunized with snake venoms to a high titre should give positive serological reaction with the homologous snake sera.

The chief difficulty in the application of these criteria rests in the fact that during capture and in captivity the snakes frequently bite themselves. Their sera shortly after capture frequently contain venom, and to avoid this and to ascertain if venom is a normal and constant constituent of the plasma, the snakes should be kept isolated and undisturbed in separate compartments for some days before bleeding out to obtain serum or plasma for experiment.

The Evidence Concerning the Presence of Constituents of the Venoms in the Plasmas of Australian Snakes.

1. Since neurotoxin is the dominant killing constituent in the colubrine venoms under consideration, we have concerned ourselves chiefly with attempts to demonstrate its presence.

It might be presumed that if sufficiently large doses of snake serum or plasma were administered subcutaneously, and if the highly diffusible neurotoxins of venom were present in the plasma, neurotoxic symptoms would be observed. Doses of citrated plasma equivalent to 4·0 cubic centimetres of fresh undiluted plasmas of the tiger snake, copper-head, death adder and black snake were given subcutaneonsly in the abdominal wall to guinea-pigs of 250 grammes weight. All these animals except that injected with tiger snake plasma survived. Those which received black snake and death adder plasmas presented an extensive area of necrosis by the sixth day, but at no time had any general symptoms. The guinea-pigs which received copper-head plasma had less striking local lesions. A guinea-pig which received four cubic centimetres of tiger

snake plasma died on the second day, but the extensive hæmorrhagic œdema of the abdominal wall was sufficient to account for this result and the symptoms presented were those of collapse and did not resemble those produced by the injection of the corresponding venom. In many guinea-pigs and rabbits smaller doses of these sera were given subcutaneously and in no case were any neurotoxic symptoms observed.

The sera were found to be more toxic when injected intraperitoneally and tiger snake plasma in doses of 1·0 to 1·5 cubic centimetres killed though not invariably in two two five hours by causing intense hæmorrhagic congestion of the bowel and serous surfaces with resultant cardiovascular collapse. Similar changes were produced with death adder plasma.

Further evidence that neurotoxin is not present in the plasma of the death adder is afforded by experiments in which citrated plasma was injected intraperitoneally in the common sand frog—*Lymnodynastes dorsalis.*

Frogs of 20 to 26 grammes were regularly killed in times varying from two to five hours with doses equivalent to 0·5 to 1·0 cubic centimetre of death adder plasma. The muscles of the leg regularly responded to faradic stimulation of the sciatic nerve with a distance of from 40 to 49 centimetres between the primary and secondary coils and when stimulated directly with the coils separated 25 to 30 centimetres. There was here no curara-like action which is regularly observed when frogs of this species are killed in about the same times with doses of death adder venom of the order of 0·1 milligramme. Under these circumstances the muscle responds when stimulated directly with the coils separated about 25 centimetres and only contracts following stimulation of the sciatic nerve when a much stronger faradic current is employed, the distance between the coils varying from 0 to 15 centimetres. In all cases the tests were carried out shortly after the animal had ceased to respire and to respond to mechanical stimuli.

It may be noted that this evidence is weakened to some extent by the possibility that the toxic substances in serum cause death too rapidly and that neurotoxin is present in too small a concentration to produce any effect on the chronaxia of muscle in the time.

As Arthus[25] has already shown, the presence of the thrombins of tiger and black snake venoms cannot be demonstrated in the sera and in our experiments doses of 0·5 to 2·0 cubic centimetres of serum or plasma from tiger snakes and black snakes produced no symptoms when injected intravenously into domestic rabbits of 1·5 kilograms.

2. If the toxic action of snake plasma be due to the presence in it of venom constituents, antivenine should have a powerful protective action. A few experiments were made with tiger snake plasma and for these I used an antivenine kindly given me by Dr. Morgan, Director of the Commonwealth Serum Laboratories, of which 1·0 cubic centimetre neutralized forty certainly lethal doses of tiger snake venom in the guinea-pig. It was, therefore, possible to use so small a dose of antivenine as to render extremely improbable any hypothetical non-specific protective effect due to horse serum proteins.

The antivenine in a dose of 0·2 or 0·25 cubic centimetre was mixed with the equivalent of 1·0 or 1·5 cubic centimetres of tiger snake plasma and after standing for one hour at room temperature the mixture was injected intraperitoneally into guinea-pigs of about 250 grammes weight. One animal which received 1·0 cubic centimetre of tiger snake plasma together with 0·2 cubic centimetre of antivenine (sufficient to neutralize eight fatal doses of venom given subcutaneously) died in three hours twenty minutes and showed the typical *post mortem* picture. Another which received 1·5 cubic centimetres of tiger snake plasma with 0·25 cubic centimetre of antivenine (sufficient to neutralize ten fatal guinea-pig doses of venom) was so sick as to appear moribund after three and a half hours and was found dead the following morning. A guinea-pig which received this dose of plasma alone died in two and a half hours and one which received this dose with 0·25 cubic centimetre of normal horse serum died in two hours twenty minutes.

Though antivenine prepared against the venoms of viperine snakes has some neutralizing effect against the hæmotoxic action of the homologous reptilian sera, univalent tiger snake antivenine affords no protection against the lethal effects produced by the intraperitoneal injection of tiger snake plasma. These effects are therefore not due to the presence of antigenic venom constituents in the plasma.

3. Using tiger snake serum injected repeatedly into guinea-pigs we have been able to produce some degree of immunity to the venom of the tiger snake and have thus confirmed Calmette's important observation of active immunization to cobra venom acquired by the injection of cobra serum. Our results are set out in Table VI.

We are not inclined to lay any great stress upon these results, which cannot, in view of other evidence, be regarded as affording proof of the constant presence in serum of venom constituents. As will be seen, most of these experiments gave negative results and only in those animals in which large doses of serum or plasma were injected, was any immunity to snake venom demonstrated. The possibility of cross immunity, independent of the presence of venom constituents in plasma, is excluded by the experiments later to be reported, but despite great care in the isolation of snakes used for bleeding, we feel uncertain whether we have wholly excluded the possibility that that venom casually present in the plasma (from self-inflicted bites or from the bites of other snakes) might really be responsible for the observed immunity. The large doses of serum or plasma necessary for the demonstration of any immunity against venom accentuate our doubts concerning the validity of such experiments for demonstration of the presence of venom constituents in the plasma.

The passive protective action of strong precipitating sera prepared by injecting rabbits repeatedly with snake sera was also tested by mixing them in doses of two to five cubic centimetres with one to one and a half certainly lethal doses of the corresponding venoms—allowing the mixtures to stand for one hour at room temperature and then injecting them into guinea-pigs. These antisera exhibited no greater degree of protection than pooled normal rabbit serum which with one or two venoms afforded protection against one certainly lethal dose (Table VII).

4. *Complement Fixation Tests with Venoms and the Sera from Rabbits Immunized with Corresponding Snake Sera to High Titres.*

For another purpose it was necessary to obtain rabbit sera giving precipitin and complement fixation reactions to a high titre with various snake

TABLE VI.

Guinea-pigs Immunized with Snake Sera and Tested by Subcutaneous Injection of Corresponding Venom a Week after the last Immunizing Injection.

Weight of Guinea-pig in Grammes.	Amount of Serum Injected in Cubic Centimetres.	Time Occupied in Immunization in Weeks.	Weight of Homologous Venom Injected Subcutaneously.	Number of Certainly Lethal Doses.	Result.
Immunized with death adder serum.					
375	6	4	0·15	2·5–3	Died in 1½ hours.
325	8	3	0·048	1	Died on the second day
Immunized with the serum of Pseudechis australis.					
350	8	4	0·7	More than 1	Died in less than 18 hours.
385	6	4	0·56	1	Died in less than 18 hours.
Immunized with copper-head serum.					
345	6	4	0·034	1·5	Died in less than 18 hours.
352	6	4	0·024	1	Died in less than 18 hours.
Immunized with black snake serum.					
342	7	4	0·48	1	Died in less than 18 hours.
Immunized with tiger snake serum.					
417	4·8	3	0·008	1	Died on the fifth day.
457	10·5	7	0·009	1	Died on the sixth day.
464	9	12	0·014	1·5	Survived.
482	9	12	0·0144	1·5	Survived.
495	9	12	0·0148	1·5	Survived.

sera. These were utilized in the protection experiments just described and also to ascertain whether any complement fixation could be obtained with the homologous venoms.

The sera in question were prepared by immunizing rabbits with the sera of tiger snakes, death adders, copper-head and black snakes. The copper-head, black snake and death adder antisera in a dilution of one in ten with dilutions of the homologous sera one in 20,000 fixed twelve, fifteen and six minimal hæmolytic doses of complement. The tiger snake antiserum in a dilution of one in ten with a dilution of the homologous serum one in 1,000 fixed twelve minimal hæmolytic doses of complement.

The venoms were tested in doses of 10 milligrammes, 2 milligrammes, 1 milligramme, 0·1 milligramme and in doses diminishing by a half to 0·012 milligramme. The antisera were diluted 1:5 for these tests. The venoms in a dose of ten milligrammes all possessed a definite anti-complementary action and fixed complement even in the absence of antisera but with none of the smaller doses was any fixation of complement observed in the presence of antisera.

Precipitin tests with antisera against the sera of the black snake, tiger snake, death adder and copper-head, whose titres to these sera were $\frac{1}{6,400}$, $\frac{1}{3,200}$, $\frac{1}{8,000}$ and $\frac{1}{6,400}$ respectively gave negative results when tested in various dilutions against the homologous venoms in doses of ten milligrammes, five milligrammes, two milligrammes, one milligramme, 0·1 and 0·01 milligramme. With some of the larger doses of venom using undiluted antisera a precipitate was obtained, but a similar precipitate was also observed with normal rabbit serum.

TABLE VII.

Protection Tests with Pooled Normal Rabbit Sera and with Sera from Rabbits Immunized with Snake Sera.

Weight of Guinea-pig in Grammes.	Serum in Cubic Centimetres.	Dose of Venom in Milligrammes.	Number of Certainly Lethal Doses.	Result.
Normal Rabbit Serum.				
298	2·0	0·01 tiger snake	1·6	Died on the second day.
284	2·0	0·03 copper-head	1·5	Died in less than 24 hours.
338	5·0	0·13 death adder	2·5	Died in less than 17 hours.
254	2·0	0·05 death adder	1·0	Survived.
339	2·0	0·7 black snake	1·5	Died in less than 20 hours.
257	3·0	0·56 black snake	1·5	Survived.
237	2·0	0·012 brown snake	1·3	Died in 22½ hours.
316	3·0	0·009 brown snake	1·0	Survived.
Snake Sera Antisera.				
257	2·0 tiger snake	0·01 tiger snake	2·0	Died on the third day.
285	2·0 tiger snake	0·03 copper-head	1·5	Died in less than 24 hours.
280	5·0 death adder	0·13 death adder	3·0	Died in less than 17 hours.
289	2·0 death adder	0·05 death adder	1·1	Survived.
278	3·0 black snake	0·56 black snake	1·4	Died on the second day.
336	2·0 black snake	0·7 black snake	1·5	Died in 3 hours.
200	2·0 brown snake	0·012 brown snake	1·3	Died in less than 20 hours.
292	3·0 brown snake	0·009 brown snake	1·0	Survived.

5. *Complement Fixation with Antivenines and the Sera from Corresponding Snakes.*

The converse experiment has been performed with the sera of rabbits immunized for more than a year with the venoms of the tiger snake, copper-head and death adder.

Of the sera in question 1·0 cubic centimetre neutralized 0·11 milligramme, 0·2 milligramme and rather more than 0·06 milligramme of the corresponding venoms as judged by protection experiments in guinea-pigs. In view of possible zone effects the sera were tested by complement fixation in a dilution of one in five against venom in doses of one milligramme, 0·5 milligramme, 0·1 milligramme and in doses diminishing by half to 0·0008 milligramme and also in a further range of doses diminishing by half from 0·01 to approximately 0·00001 milligramme. The tiger snake antivenine failed to react with the venom in any dilution tested, but the death adder and copper-head venoms reacted in moderately narrow zones with their corresponding antivenines (death adder venom from 0·00125 milligramme to 0·0003 milligramme, copper-head venom from 0·005 milligramme to 0·0003 milligramme).

These two last antivenines were also tested to determine the amount of complement fixed by venom. In the case of the death adder, antivenine diluted one in five with 0·001 and 0·005 milligramme of venom fixed three minimal hæmolytic doses of complement and in that of the copper-head, antivenine similarly diluted with 0·001 milligramme of venom fixed between six and eight minimal hæmolytic doses of complement. When the corresponding snake sera heated for fifteen minutes at 56° C. were tested in dilutions of one in 2·5, one in five, one in 7·5 and one in ten with copper-head and death adder antivenines diluted one in five no complement fixation could be detected using three minimal hæmolytic doses of complement.

These two sets of results with serum antisera and antivenine tested for complement fixation against venom and corresponding snake sera, do not furnish strong evidence of the absence of antigenic constituents of venom from plasma, since zone phenomena might conceivably account for the negative results obtained, though care has been taken to avoid this possibility.

Summarizing all this evidence, it appears that the toxicity of snake plasma cannot be accounted for by the constant presence of toxic constituents of venom. Neither neurotoxin nor thrombin can be demonstrated in the plasma of the tiger snake, nor is there any certainty that antigenic constituents of venom are normally present in snake plasma.

There remain for consideration the very important experiments of Phisalix and Bertrand,[16] who clearly demonstrated some loss of toxicity in defibrinated viper blood from snakes whose venom glands had been removed some time previously—fifty-two and sixty-seven days. This seems almost conclusive proof that some part of the toxicity of the serum of vipers is due to the activity of the venom glands. The vipers, however, did not feed after the operation and became very wasted, yielding but little blood when killed. To what extent these factors may have operated in diminishing the toxicity of the serum is uncertain, nor is it clear in the only two papers to which I have had access whether any special precautions were necessary to keep the control snakes from biting each other, or to what extent the toxicity of normal viper serum is due to the presence of venom from this cause.

In our experience the plasma of recently caught snakes, which have been bitten during capture or transport, becomes less toxic when the snakes are isolated for a few days, and except when administered intraperitoneally the serum or plasma of such isolated snakes has very little toxicity. The results of our experiments upon the effect of excision of the venom glands on the toxicity of the plasma, as estimated by intraperitoneal injection in guinea-pigs, were wholly negative.

The venom glands of a number of healthy tiger snakes were excised under full ether anæsthesia. The vessels supplying the gland were not ligated, but hæmostasis was secured by external pressure with rubber bands for ten or twelve hours after the operation. The experiments were complicated by regeneration and after a few weeks enough venom was produced by some of the experimental snakes to kill mice and guinea-pigs which they were allowed to bite.

In Table VIII there are set out the results of the intraperitoneal injection of the plasma of normal tiger snakes and of that obtained from some of the experimental snakes by bleeding them out under ether anæsthesia 63, 74, 110 and 139 days after the

TABLE VIII.

Comparison of Toxicity of Snake Plasma from Normal Tiger Snakes and from Snakes in which the Venom Glands had been Excised 63 Days, 74 Days, 110 Days, and 139 Days Earlier.

Number of Guinea-pigs.	Dose of Plasma (Intraperitoneally).	Result.
	Normal.	
1	1·5	Died in 2½ hours.
4	1·0	One died in 1 hour 50 minutes, one in 5½ hours, and two had severe symptoms but survived.
2	0·75	One died in less than 24 hours and one had severe symptoms but survived.
2	0·5	One died in less than 20 hours and one had moderate symptoms but survived.
	Excised Glands—63 Days. (No functional regeneration of glands.)	
1	1·5	Severe immediate symptoms; killed when moribund on fifth day.
3	1·0	One died in 1 hour 40 minutes, one in 4 hours, and one had severe symptoms but survived.
2	0·75	One died on the second and one on the third day.
1	0·5	Died in 2½ hours.
	Excised Glands—74 Days. (No functional regeneration of glands.)	
2	1·5	Died in 2½ hours.
4	1·0	One died in 3½, one in 4, and one in 5 hours, and one survived.
1	0·5	Severe early symptoms, but survived.
1	4·0 (subcutaneous)	Died on the second day.
	Excised Glands—110 Days. (Killed a mouse in 1 hour on the forty-seventh day, in 10 minutes on the sixty-third day.)	
1	1·5	Died in 2½ hours.
2	1·0	One died in less than 16 and one in 27 hours.
1	0·5	Died in less than 22 hours.
	Excised Glands—139 Days. (No functional regeneration of glands.)	
2	1·0	One died in less than 16 and one in less than 22 hours.
1	0·5	Severe early symptoms, but survived.

operation. It will be seen that irrespective of functional regeneration of the venom apparatus, the toxicity of the plasma of these snakes did not differ appreciably from that of snakes with intact venom glands. All the guinea-pigs showed the same symptoms, swelling of the abdomen within a few minutes, followed by collapse and usually by death, and the same typical picture of congestion of the abdominal viscera was seen in all of those which died. This irritative action of the plasma of the Australian snakes has clearly nothing whatever to do with the presence or absence of the venom glands.

It is of some interest that nearly all our operated snakes were able to digest their food, despite their inability to inject any appreciable quantity of venom into their prey.

The evidence brought forward here makes it impossible for us to accept the hypothesis of Phisalix and Bertrand or even that of Calmette as the explanation of the occurrence of immunity in the Australian venomous snakes. There remains, however, a third possibility. The one certain method by which venom can gain access to the circulating blood is by bites either self-inflicted or by other reptiles. There is no sound volume of evidence to indicate the frequency of these accidents in the course of the struggle for food or during mating, but in captivity they are extremely common.

Most Australian reptiles exhibit their annoyance by biting themselves if they can find no more convenient object into which to discharge their venom. In the field, snakes almost invariably bite themselves during capture, unless taken by hand, and bite also their fellow captives, so that if "milked" soon after being caught they usually yield but little venom. Their plasma also is highly toxic when injected subcutaneously, but this toxicity diminishes greatly if they are isolated for a few days. Snakes sometimes bite through the floor of the mouth by closing the jaws with the fangs still partially erect, and these wounds are occasionally seen.

In captivity the reptiles of different species are kept segregated so as to avoid the injection of venom of one species into individuals of another, though we have shown that the venom of copper-heads repeatedly bitten by tiger snakes does not thereby acquire any "thrombin" and is not quantitatively altered in toxicity. For the experiments recorded here segregation was obviously essential.

In Nature the incidence of snake bites by snakes of other species must be low, since they are only likely to occur when two snakes are in pursuit of the same prey and since the snake population is never very dense, individuals of different species being rarely found together or close to each other except in flood time. In the field, Mr. T. Eades, who has had thirty years' experience of snake catching, has only once seen a black snake engaged in swallowing a small tiger snake.

It might be argued that in the struggle for existence only those individuals which possessed immunity to the venom of snakes with the same geographical distribution tended to survive and propagate their kind. Such an explanation would account for the relatively low resistance exhibited by the tiger snake and death adder to the venom of the cobra, but does not account for the non-specific immunity exhibited by the Australian elapines on the basis of their present geographical distribution. If the immunity of the tiger snake and death adder were dependent upon propinquity, the death adder ought to exhibit immunity to black snake rather than to tiger snake venom and the tiger snake should be more immune to the venoms of the copper-head and black snake than to that of the death adder. However, the geographical distribution of these species was probably quite different at an earlier stage in the history of Australia, and it seems probable that the immunity which these reptiles display to venoms other than their own is determined by their close serological relationship and that immunity to the homologous venom necessarily involves some degree of immunity to the venoms of closely related species. The lower resistance of the copper-head and tiger snake to the venoms of the black snake and cobra is probably dependent more upon the differences in the toxic constitution of their venoms than upon their geographical distribution.

I have already suggested that the immunity of the mongoose, hedgehog and dormouse may be dependent upon their intimate association with venomous reptiles and the high immunity of the non-venomous snakes may also be related to a similar circumstance. They share with the venomous species a common food supply (small rodents and marsupials), and opportunity for conflict is thus provided.

The Nature of the Immunity of Venomous Snakes.

The substantial nature of the immunity of venomous snakes is shown not only by the fact that they are able to withstand large doses of venom injected subcutaneously which would be absorbed only slowly and would allow time for reserve protective mechanisms to come into operation, but they can also survive without symptoms the intravenous or intraarterial injection of doses of venom of the order of 20 to 50 milligrammes. The question at once arises as to whether antivenomous action of the plasma is alone sufficient to account for this immunity.

The Extent to which Protection is Accounted for by the Antivenomous Action of the Plasma.

The degree of the protection afforded by the serum of Australian snakes heated to 58° C. for thirty minutes and tested by subcutaneous injection into guinea-pigs of 250 grammes weight is indicated by a few experiments, the results of which are set out in Table IX. The sera injected alone caused only slight local effects in a dose of 2·0 cubic centimetres. Mixtures of venom and sera were allowed to stand for one hour at room temperature before injection.

TABLE IX.

The Protective Effect of Australian Snake Sera.

Quantity and Type of Serum.	Dose of Venom in Milligrammes.	Result.
Copper-head:		
0·15	0·06 copper-head	Died in less than 18 hours.
0·3	0·06 "	Died on the third day.
0·4	0·06 "	Died on the third day.
0·5	0·06 "	Survived.
1·0	0·06 "	Survived.
Tiger snake:		
0·1	0·1 tiger snake	Died in less than 18 hours.
0·2	0·1 "	Died in less than 18 hours.
0·25	0·02 "	Died on the sixth day.
0·3	0·02 "	Died on the fourth day.
0·25	0·06 copper-head	Survived.
Carpet snake:		
1·0	0·02 tiger snake	Died on the third day.
1·5	0·02 "	One survived and one died in less than 24 hours.
2·0	0·02 "	One survived and one died in 50 hours.
1·0	0·06 copper-head	Died on the second day.
1·5	0·06 "	Died on the second day.
2·0	0·06 "	One died on the first and one on the third day.

The protective effect of carpet snake serum is slight, 2·0 cubic centimetres not affording complete protection against four certainly lethal doses of tiger snake and three certainly lethal doses of copper-head venom. The sample of tiger snake serum used failed in a dose of 0·3 cubic centimetre to protect against four certainly lethal doses of tiger snake venom, but 0·25 cubic centimetre protected against three certainly lethal doses of copper-head venom. The copper-head serum in a dose of 0·5 cubic centimetre protected against the same dose of this last venom.

In order to obtain an approximate estimate of the amount of venom which could be dealt with by the antivenomous action of the plasma, the following experiment was performed.

A tiger snake weighing 200 grammes was anæsthetized with ether and two cannulæ of about the same bore were tied into the left arch of the aorta, one directed proximally and one distally. The snake was bled out through the proximal cannula into ten cubic centimetres of 2% citrate saline solution. Oxygenated Ringer's solution was then allowed to flow distally into the aorta through the other cannula by gravity at 35 millimetres of mercury pressure. The snake was thoroughly perfused for one and a quarter hours and three consecutive amounts of 300 cubic centimetres of perfusate were collected, the last sample containing only a very few blood corpuscles.

The citrated plasma and the three samples of perfusate were heated to 58° C. for half an hour and then tested by protection experiments in guinea-pigs of 200 grammes weight, with the following results.

Protective Power of the Plasma.—The total volume of the citrated plasma was 20 cubic centimetres. Varying amounts of this were mixed with 0·06 milligramme of copper-head venom and after standing for one hour at room temperature, 18° C., the mixtures were injected into guinea-pigs with the following results:

Volume of Citrated Plasma in Cubic Centimetres.	Result.
1·0	No symptoms.
0·8	No symptoms.
0·6	Died on the fifth day.
0·4	Died in less than 15 hours.
0·2	Died in less than 6 hours.

Of citrated plasma, 0·6 cubic centimetre neutralized 0·06 – 0·013 = 0·047 milligramme of copper-head venom. The total neutralizing capacity of the volume of plasma collected was therefore 1·56 milligramme of copper-head venom.

Protective Power of Sample I of Perfusate.—This was mixed in varying quantities with 0·04 milligramme of copper-head venom.

Volume of Perfusate in Cubic Centimetres.	Result.
10	No symptoms.
8	No symptoms.
5	Died in 24 hours.
2	Died in less than 15 hours.

Of the first sample of 300 cubic centimetres of perfusate five cubic centimetres did not quite neutralize 0·04 – 0·013 = 0·027 milligramme of venom. The whole sample 300 cubic centimetres could therefore neutralize about 1·62 milligrammes of venom.

The protective power of the second and third perfusion samples was negligible. A mixture of 15 cubic centimetres of the second sample with 0·04 milligramme of copper-head venom caused death in six and a half hours (the average death time with guinea-pigs of about 200 grammes receiving this dose of venom alone being approximately six hours).

Assuming that the second sample had one-sixth the protective power of the first (a very liberal assumption), the total protective power of all the plasma in the reptile's body would be 1·56 + 1·62 + 0·27, or approximately 3·45 milligrammes of venom. Now since snakes of this size and species regularly tolerate without symptoms more than 20 milligrammes of this venom injected intravenously, their tolerance cannot depend wholly upon the protective properties of the plasma, though it might be argued that in heating the plasma some destruction of its protective properties occurs. Even if this be so, alternative evidence that the plasma does not suffice to neutralize all the injected venom is provided by an increase in the toxicity of the plasma, which immediately follows the injection of doses of venom of the order of 20 milligrammes intravenously.

The Rate of Disappearance of Injected Venom from the Circulation.

This added toxicity of the plasma, which is clearly due to unneutralized venom, gradually disappears in the course of two or three days, and occurs equally rapidly in snakes in which the venom glands have been removed or in which the Wolffian ducts with the afferent renal veins have been tied. It is clear, therefore, that the added venom is not selectively removed either by the venom glands or through the urinary tract. To illustrate this very regular phenomenon I have selected as an example an experi-

ment in a tiger snake in which the Wolffian ducts and the afferent renal portal veins had been tied three days previously.

Effects of Ligature of Wolffian Ducts on Removal of Injected Venom.

Tiger snake, 250 grammes.

On July 11, 1930, the Wolffian ducts, together with afferent renal portal veins, were tied under ether anæsthesia.

On July 14, 1930, under ether anæsthesia a sample of blood was removed from the inferior *vena cava*, 20 milligrammes of copper-head venom in one cubic centimetre of saline solution were injected peripherally into the left arch of the aorta and samples of about 1·0 cubic centimetre of blood were removed from the inferior *vena cava* and immediately diluted with an equal volume of 1% citrate saline solution, twenty minutes, four hours, twenty-six hours and seventy-two hours later. The snake remained in splendid condition till July 29, 1930, but died unexpectedly on July 30, 1930. After separation of the red blood corpuscles by centrifugation, the diluted plasma of the samples was heated at 58° C. for 30 minutes to destroy its natural toxicity. The injection in guinea-pigs of 200 grammes of various amounts of plasma from the samples gave the following results expressed in terms of undiluted plasma.

Sample I (before the injection)—
0·5 cubic centimetre caused no symptoms.

Sample II (twenty minutes after injection)—
0·2 cubic centimetre killed in 3¾ hours.
0·1 „ „ „ „ 7¼ „
0·05 „ „ „ „ 12 „
0·025 „ „ „ „ 30 „
0·01 „ „ caused no symptoms.

Sample III (four hours after injection)—
0·3 cubic centimetre killed in 7¾ hours.
0·2 „ „ „ „ less than 17 hours.
0·1 „ „ „ „ 24½ hours.
0·05 „ „ „ „ 51 „

Sample IV (twenty-six hours after injection)—
0·5 cubic centimetre killed in 3¾ hours.
0·2 „ „ caused no symptoms.

Sample V (seventy-two hours after injection)—
0·5 cubic centimetre caused no symptoms.

The toxicity of the plasma of which, twenty minutes after the injection, 0·025 cubic centimetre contained more than one unbound lethal dose of copper-head venom (some being neutralized by the snake plasma), had diminished by half within four hours. After twenty-six hours about three-fourths of the toxicity had been lost and after seventy-two hours the heated plasma had the same order of toxicity as the sample obtained before the injection of venom. Assuming that the antivenomous substances of the plasma neutralized about four milligrammes of the total dose of 20 milligrammes of copper-head venom injected, 16 milligrammes of venom remain to be accounted for.

Is the Venom Destroyed by Enzyme Action of Some Constituent of the Plasma?

Before proceeding further it is necessary to put forward evidence which shows that the methods of titration used are sound and that the disappearance of venom is not due to some action of the plasma on the venom causing it to become heat labile. Phisalix[26] claims that this is the case when viper venom is added to viper serum and the mixture heated to 58° C. The following experiment eliminates this possibility in the case of copper-head venom mixed with tiger snake plasma and incidentally excludes the further possibility that the disappearance of the venom is due to destruction by enzyme action by the plasma.

Fresh tiger snake plasma aseptically collected was mixed with copper-head venom in sterile saline solution (2·0 milligrammes per cubic centimetre) so as to be in the proportion 2·5 cubic centimetres plasma, diluted with an equal volume of 2% citrate saline solution and 2·0 cubic centimetres of venom solution, the total volume being 7·0 cubic centimetres and the content of venom 0·57 milligramme per cubic centimetre. Portions of this mixture were taken out from time to time and injected into guinea-pigs in varying doses both unheated and heated at 58° C. for 30 minutes. The results are set out in Table X.

There is no evidence of any progressive loss of toxicity by prolonged contact with a fixed volume of plasma under aseptic conditions, but there is some slight loss of toxicity of the venom caused by heating for half an hour at 58° C. Contact with the plasma does not convert the venom into a heat labile form, since the amount of destruction of neurotoxin is no greater than occurs with this venom when heated without the addition of plasma.

The experiment also indicates the extent to which the copper-head venom is neutralized by this sample

TABLE X.

Time of Contact.	Dose in Cubic Centimetres.	Results of Injection.	
		Unheated.	Heated at 58° C.
½ hour at 17·5° C.	0·05	No symptoms.	No symptoms.
	0·1	Moderate symptoms survived.	No symptoms.
	0·15	—	Died on the third day.
	0·2	—	Died on the first day.
2¾ hours at 17·5° C.	0·15	—	Died on the third day.
	0·2	Died on first day.	Died on the first day.
20 hours at 17·5° C.	0·15	—	Died on the fourth day.
	0·2	Died on first day.	Died on the first day.
	0·3	Died in 3 hours.	—
20 hours at 17·5° C. and 24 hours at 2° C.	0·2	Died on first day.	Died on the second day.

of tiger snake plasma. The lethal dose of venom for guinea-pigs of the weight used is about 0·015 milligramme and the lethal dose of the mixture was about 0·15 cubic centimetre, which actually contained 0·038 milligramme of copper-head venom. This dose contains about 0·13 cubic centimetre of plasma which therefore neutralizes rather more than one certainly lethal dose of copper-head venom.

Two questions at once arise from the consideration of these results. Upon what does the disappearance of toxicity from the plasma of a snake into which venom has been injected intravascularly depend? And why does the presence for a considerable period of a high concentration of venom in the blood fail to produce symptoms?

What Causes the Disappearance of Venom from the Snake's Plasma?

There are here three main possibilities: (i) The venom may be excreted by the skin into the alimentary tract, by the venom glands or other secreting glands or by the urinary system; (ii) it may be absorbed by the tissues or destroyed by them without causing symptoms; or (iii) further antitoxic substances may be generated by the tissues to neutralize or destroy it.

Taking first the possibility of excretion. We have already mentioned the exclusion of the venom glands and the urinary tract as channels of excretion. Excretion of venom by the skin and by the alimentary tract are difficult of investigation. We have made no attempt to attack the former problem, and the methods used for the investigation of the latter could be expected to give positive results only if the greater part of the injected venom were excreted by this channel. Our experience in recovering only one-thirtieth of a large dose of venom administered orally did not make us hopeful about the possibility of detecting any small quantities of venom excreted into the alimentary tract, but in three tiger snakes (in one of which the venom glands had been removed a month earlier) we injected 20 milligrammes of copper-head venom intravenously and examined the excreta before the injection and daily from the first to the seventh day afterwards. The samples of excreta were diluted one in ten, filtered through a Seitz filter and injected in doses of one to two cubic centimetres of the diluted filtrate (equivalent to 0·1 to 0·2 cubic centimetre of excreta). In these doses the excreta of normal tiger snakes never causes any symptoms in guinea-pigs of 200 grammes. All our experimental tests were also negative except that of a sample of excreta obtained on the second day, of which 1·5 cubic centimetres caused no symptoms and 2·0 cubic centimetres killed a guinea-pig in twenty-four hours. Unfortunately no more filtrate was available to ascertain whether this death was only a chance one or whether the toxic substance present could be neutralized by copper-head antivenine. Since our results were otherwise negative, no stress can be laid on them, and we cannot exclude the possibility of some excretion of venom into the alimentary canal and its subsequent destruction by ferment and bacterial action.

For the investigation of the second possibility two methods were available—the study of the absorption or destruction of venom by perfused and minced tissues *in vitro*, and that of perfusion experiments in the living snake in which the plasma had been removed and replaced by an artificial plasma of Ringer solution containing gum.

Absorption experiments were carried out with thoroughly perfused snake tissues minced aseptically with sharp scissors and left in contact with venom dissolved in sterile saline solution at 0° C. for fourteen, twenty and forty hours. The Ringer's solution used for perfusion and making up the venom was buffered either with boric acid and borate to pH 7·6 (Trevan) or with bicarbonate. The former is perhaps preferable as it has a slight bacteriostatic action. All experiments in which any bacterial growth took place were discarded. Control venom solutions diluted to a similar extent with Ringer's solution showed no loss of potency in forty hours at 0° C. The amount of venom finally present in the supernatant fluid after absorption was determined by injecting in groups of 20 mice, of average weight 20 grammes, a dose estimated to contain about one certainly lethal dose of venom. The amount of free venom actually present was then read off the "characteristic" of the venom.

In Table XI are set out the results of such an experiment in which minced muscle from a tiger snake perfused with 600 cubic centimetres of Ringer's solution was put up with tiger snake venom alone and with venom and plasma, and allowed to stand forty hours at 0° C. A dose of 0·2 cubic centimetre of the supernatant fluid from each of the mixtures diluted one in ten was injected into mice. This dose should have been capable of causing 80% mortality in mice.

TABLE XI.

Absorption in Vitro by Snake Muscle.

Group.	Tiger Snake Venom (1 Milligramme per Cubic Centimetre).	Plasma.	Saline Solution.	Muscle.	Percentage Mortality in Mice.
A ..	0·5 c.cm.	—	0·5 c.cm.	1·0 gramme	5·0
B ..	0·5 c.cm.	0·5 c.cm.	—	1·0 gramme	5·0
C ..	0·5 c.cm.	0·5 c.cm.	1·0 c.cm.	—	50·0
D ..	0·5 c.cm.	—	1·5 c.cm.	—	70·0

Reading the dose of venom corresponding to these percentage mortalities from the "characteristic" of the venom for mice (Kellaway[27]), in the dose administered there was 0·0045 milligramme of tiger venom in solution D and less than 0·002 milligramme of active venom in mixture A. There was, therefore, a loss by absorption, neutralization or enzyme action of 60% of the venom. The presence of plasma did not cause any obvious additional neutralization or destruction of venom.

A number of absorption experiments were carried out and invariably gave positive results. The tissues used caused variable amounts of loss—kidney, heart, muscle, spleen and brain from 50% to 70%, liver about 30%. The washed red blood corpuscles of the snake caused no loss by absorption or neutralization.

Control experiments were carried out, using the perfused tissues of a susceptible animal—the guinea-pig. These showed loss of toxicity in the supernatant fluid of a similar order to that found in the experiments with snake tissues. While it cannot be assumed that the loss observed in the two groups of experiments is due to the same causes, the results in the latter group discount the value of the former as affording any indication of what happens when venom is introduced into the circulation of the living reptile.

These absorption experiments cannot therefore be used to exclude the possibility that the high immunity of snakes to their own and allied venoms depends in large part upon the inability of living snake tissues to fix venom; nor can they be held to decide in favour of the differential absorption or destruction of venom by those living snake tissues which are not essential to life as a means of protection of the central nervous system from effective concentrations of venom.

In contrast to these results were those of perfusion experiments which were uniformly negative, though, as will be seen, the time during which observations could be made was only two and a half to three hours. It should be pointed out, however, that during this time a very considerable loss of toxicity occurs following the introduction of venom into the circulation of the intact reptile, and that unless the coincident œdema of the tissues causes much concentration of venom in the circulating fluid, the negative evidence of these perfusion experiments must be taken into account as indicating the improbability of fixation of venom to living tissues as a means for its removal from the circulating blood.

Perfusion Experiments.

Perfusion experiments were carried out by bleeding out snakes and perfusing them with Ringer's solution containing gum arabic. After perfusion, a limited amount of Ringer's solution was kept in circulation through the snake and the washed red blood corpuscles were added to this artificial circulating fluid which was kept oxygenated by passing a steady stream of oxygen through the reservoir. This type of experiment was used for two purposes: (i) to ascertain whether venom added to the system was lost by elimination, absorption or destruction by the tissues and (ii) to discover whether without addition of venom any additional antitoxic substances were liberated into the circulating fluid. The following protocol gives details of the technique used in these experiments.

Tiger Snake.—Weight before experiment was 168 grammes, weight after experiment was 210 grammes, gain in weight by œdema was 42 grammes. Room temperature was 21° C. Rate of heart beat throughout experiment was 44 per minute. Under full ether anæsthesia the heart and great vessels were exposed by cutting through several abdominal plates. Two cannulæ of equal bore were introduced into the inferior *vena cava*, one directed towards the heart and the other peripherally. The former was connected with a small reservoir containing Ringer's solution which was supplied at a pressure head of four to five centimetres of water pressure. The Ringer's solution contained 0·5 cubic centimetre of 24% calcium chloride and 50 cubic centimetres of *mucilago acaciæ* per litre and its pH was 7·6. The fluid flowing from the distal cannula was collected and the first 150 cubic centimetres were discarded after centrifuging down the red blood corpuscles. These, after they had been washed, were added to the Ringer's solution in the reservoir which was kept oxygenated by a gentle stream of oxygen. The fluid flowing out of the distal cannula was now collected and replaced in the reservoir from time to time. The volume of fluid in circulation was sixty cubic centimetres together with that contained in the vascular system of the snake (about thirteen cubic centimetres). It progressively diminished during the experiment, being retained in the body of the snake.

The following figures (Table XII) trace this loss to the end of the experiment when it amounted to forty cubic centimetres *plus* about ten cubic centimetres removed as samples for investigation at various times during the experiment.

TABLE XII.

Time.	Volume of Fluid in Circulation.	Rate of Flow.	Circulation Time in Minutes.
4.32 p.m.	73	5	14·6
5.32 ,,	58	4	14·5
6.4 ,,	50	3·5	14·3
6.32 ,,	37	3·4	10·3
6.47 ,,	30	3·75	8
7.2 ,,	22	—	—

In this experiment five milligrammes of tiger snake venom were placed in the reservoir at 4.32 p.m. and at 4.57 p.m. the first sample of fluid was taken—sufficient time being thus allowed for admixture of the venom.

The experiment was discontinued when there was no longer sufficient fluid to maintain the circulation. The addition of venom caused temporary cessation of respiration and loss of sensitiveness to mechanical stimuli. At the end of the experiment this snake was still breathing and had recovered to some extent as judged by its reaction to stimuli. The samples were kept at room temperature until tested at the end of the experiment by injection in suitable dosage into guinea-pigs.

Perfusion fluid in experiments in which no venom was added, was not toxic to guinea-pigs of 200 to 250 grammes in doses of 0·5 to 2·0 cubic centimetres, but was not tested in larger doses. In none of these experiments was there any loss of toxicity two and a half to three and a half hours after the first sample was taken for testing, which could not be accounted for by the slight increase in protective power demonstrable in samples taken at similar times in experiments in which no venom had been added to the circulating fluid. In the experiment quoted above the sample taken at 4.57 p.m. and the final sample gave the following results (Table XIII) when diluted one in five and injected subcutaneously into guinea-pigs.

TABLE XIII.

Sample.	Number of Animals.	Dose in Cubic Centimetres.	Result.
Initial ..	2	0·8	Died on the fourth day.
	2	0·6	Both survived.
	2	0·4	One died on the eighth day and one survived.
Final ..	2	0·8	Died on the fourth day.
	2	0·6	One died on the seventh day and one survived.
	2	0·4	One died on the fourth day and one on the eighth day.

The numbers of animals are too small in view of the variation in the killing dose. Obviously much of the introduced venom was neutralized in the first sample, since, had there been no loss of toxicity, two to three certainly lethal doses of tiger snake venom must have been present in 0·8 cubic centimetre of the one in five dilution. This and other similar experiments demonstrated no striking further loss of toxicity during the course of the perfusion.

Control experiments showed that the method of oxygenation did not cause any loss of venom and further control experiments in which no venom was added, showed some increase in the antitoxic power of the circulating fluid during the course of the experiment. Various doses of undiluted fluid after removing the red blood cells by centrifugation were allowed to stand for one hour at room temperature with 0·01 milligramme of tiger snake venom (about two and a half lethal doses for guinea-pigs of 200 grammes weight) and the mixtures were injected into animals with the following results (Table XIV).

TABLE XIV.

Sample.	Dose of Fluid in Cubic Centimetres.	Result.
Initial ..	0·7	Died on the seventh day.
	0·5	Died on the fourth day.
	0·2	Died on the second day.
Final.. ..	0·7 }	Survived without symptoms.
	0·5 }	
	0·3	Died on the seventh day.
	0·2	Died on the fourth day.

In discussing the significance of these perfusion experiments, it is important to realize that the absorption of water and salts from the artificial perfusion fluid may give rise to concentration either of venom, of antitoxic substance or of both. This may be held to account for the apparent increase in antitoxic substances during the course of the perfusion and may also prevent detection of loss of venom by masking any change which occurs. It is perhaps significant that in one or two experiments the perfusion fluid at the end of the experiment appeared to contain a slightly increased concentration of venom.

In these and in other experiments in which living snakes were perfused through the aorta, it was found that the reptiles rapidly became paralysed and lost their sensitiveness to mechanical stimuli, following the injection of doses of venom very much smaller than sufficed to cause similar effects when injected intravenously in the normal reptile. This increased sensitiveness is too great to be accounted for wholly by loss of the protective power of the plasma, and must be in part related to œdema and imperfect oxygenation of the tissues.

At an earlier stage in the investigation some experiments were made in the hope of discovering whether the liver could detoxicate venom. It was not possible to excise this organ, and we therefore attempted to exclude it, together with the other organs in the posterior part of the body, by tying the aorta and inferior *vena cava* at the cranial pole of the liver. It was thought that doses of venom which have no obvious effect when injected intravascularly in the intact reptile, might cause paralysis in the head end of such a preparation if the liver were important as a detoxicating organ and if it were put out of action. The operation is well supported by normal snakes if no venom is injected, the reptiles surviving about two days in active condition and dying on the third or fourth day.

The results of the injection of venom did not suggest that the liver has any power of destroying venom. The anterior part of the snake did not become paralysed if venom were injected cranial to the ligatures in doses of 10 to 20 milligrammes, but if a second dose of the same size were injected cranially, paralysis commenced in the tip of the tail and spread forward towards the region of the ligature.

After the injection of venom into the forward part of the circulation it rapidly disappears. For example, in a tiger snake one and a half hours after the injection of 20 milligrammes of copper-head venom a dose of 0·5 cubic centimetre of plasma was not toxic for guinea-pigs of 250 grammes weight, whereas shortly after the injection 0·3 cubic centimetre of plasma caused death in guinea-pigs of this weight. The increased toxicity caused by a second injection was not so rapidly diminished as following the first injection.

The disappearance of venom from the circulation of the anterior part of the reptile in these experiments without any obviously higher concentration being detected in the "posterior" blood might conceivably be due to a difference in the protective power of "anterior" and "posterior" blood. This possibility was investigated, but no difference could be discovered between samples taken from the anterior and posterior circulations four hours after ligation of the aorta and inferior *vena cava* in a snake in which no venom had been injected.

In other experiments trypan blue 1·0 cubic centimetre of 1% solution was injected into the anterior circulation and its fairly rapid disappearance was observed by colorimetry. Expressing the amount of dye present in the aortic blood ten minutes after the injection cranially into the inferior *vena cava* as 100, after forty minutes it was 56, after four hours 27, after six hours 21 and after twenty-five hours 16. In the posterior circulation values of 16 were obtained for inferior *vena cava* blood forty minutes and four hours after the injection.

A uniform feature in these ligation experiments was the loss of red blood cells from the circulation in the anterior part of the body and the gain in red blood cells in the blood of the posterior part of the body. Independent of any loss by sampling, the samples from the inferior *vena cava* (posterior blood) showed an increasing content of red blood corpuscles and those from the aorta (anterior blood) a decreasing content. This posterior part of the circulation appeared to be maintained, though feebly, by two sets of collaterals—through the vessels of the body wall and spinal cord and through the lung vessels. The accumulation of red corpuscles

in the posterior circulation was virtually a sedimentation in a very sluggishly moving current of blood.

Venom is not lost from the anterior to the posterior circulation by transport on red blood corpuscles, for the corpuscles from 1·0 cubic centimetre of the blood of envenomed snakes, either immediately or some time after the injection of venom, failed to cause any symptoms when injected subcutaneously into guinea-pigs and *in vitro* red cells failed to absorb any appreciable quantity of venom.

If venom is injected into the posterior circulation in doses of the order of 10 to 20 milligrammes, rapid paralysis ensues, commencing at the tip of the tail and spreading to the region of ligature. It appears that the nervous tissues are rapidly affected by venom when their blood supply is insufficient.

The only evidence of any considerable loss of venom from the anterior to the posterior circulation is afforded by the onset of paralysis in the hinder region following injection of venom into the anterior circulation, and in these experiments venom cannot be demonstrated in high concentration in "posterior blood." Possibly these poorly oxygenated tissues can absorb venom more rapidly than the well oxygenated tissues of the anterior part of the body, though the evidence of our perfusion experiments and the distribution of trypan blue in the tissues are unfavourable to this view.

Without doubt the most important factor in the immunity of snakes to their own venom is the resistance of the tissues of the central nervous system[1] to the action of venom, even in high concentrations. Phisalix held that the rapid onset of paralysis following subdural injection of small amounts of venom was proof that the central nervous tissues did not possess such an immunity. This inference is, however, not justified by his experimental data, for the injection of even two to four milligrammes of viper venom subdurally must result in a concentration of venom near the vital centres greatly in excess of that achieved by the injection of many times this dose intraperitoneally or intravenously.

When a sufficient dose of venom is injected intravenously in the intact tiger snake, paralysis of the head end with loss of response to stimuli quickly appears. For example, a dose of 50 milligrammes of copper-head venom was injected intravenously into the inferior *vena cava* of a tiger snake weighing 265 grammes. Nearly two hours later, since no symptoms had then appeared, a second dose of 50 milligrammes was given, and within a quarter of an hour the head end of the reptile was immobilized. The paralysis spread caudally, respiration becoming difficult and ineffective within twenty-five minutes, though the tail of the snake was still sensitive and capable of active movement forty minutes after the second injection, at a time when respiration had practically ceased. The reptile was no longer capable of any reflex response after four and a half hours.

It seems that a certain time is necessary for the spread of the paralysis, death occurring from failure of respiration. The time necessary for action on the tissues of the central nervous system is longer than in warm blooded animals, and thus opportunity is afforded for the removal or destruction of venom. Effective action on the central nervous system requires a high concentration of venom or a prolonged time of action.

There remains for consideration the question of the nature of the antivenomous bodies in the plasma. On *a priori* grounds it does not appear probable that they are identical with the antitoxins produced in other species in response to the injection of snake venom, and indeed there is some evidence that their nature is wholly different. The injection of a large dose of snake venom does not appear to increase the protective power of the plasma by acting as a secondary stimulus.

The protective power of the plasma from a tiger snake into which a dose of 20 milligrammes of copper-head venom was injected intravenously, was tested before the injection and on the fourth, six, ninth and fourteenth days afterwards. The smallest volume of plasma which mixed *in vitro* with 0·06 milligramme of copper-head (four certainly lethal doses) rendered it non-lethal when injected into guinea-pigs of 200 grammes weight, was before the injection 0·06 cubic centimetre, on the fourth day 0·3 cubic centimetre, on the sixth day 0·1 cubic centimetre, on the ninth day 0·1 cubic centimetre and on the fourteenth day 0·1 cubic centimetre. Possibly all the injected venom had not been eliminated or destroyed at the end of this period, thus accounting for the somewhat lower protective power of the later samples.

Summing up the evidence presented here it appears that the natural immunity of Australian snakes to their own venom is evolved as a protection to accidental bites and less probably also to the possibility of absorption of venom from abrasions in the alimentary tract. This immunity depends only in part upon the protective power of the plasma which contains antivenomous substances. The central nervous system possesses a high natural resistance to the action even of high concentrations of the venom, and there is some additional mechanism as yet unexplained which may involve some further production or mobilization of antivenomous substances and which permits of the rapid neutralization or destruction of injected venom.

[1] Houssay and his colleagues believe that in the amphibia, snake venoms are predominantly muscular poisons. If this be so in the reptilia also their high immunity to venoms may be found to depend on the resistance of their muscular tissues.

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Reports of Cases.

FOREIGN BODIES IN THE BRONCHI.

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Case I.

VERA —, when nine years of age, "swallowed" a piece of rubber. It was not recovered from the bowel and the mother concluded that the girl had coughed it up. For five years she suffered from a persistent, purposeless cough. She was seen after this lapse of time and an X ray examination of the chest failed to reveal any definite foreign body or any abnormality of the lungs. Two years later the patient came under my care with the above history.

The girl complained of a recurrent cough, and maintained that at these times she could taste rubber. The breathing was of a peculiar croupy type, and there were indefinite signs over the left hilar region. She was again sent to Sydney and a further radiographic examination was made, but without any definite findings. An asthmatic condition was suspected, and several teeth were extracted as possible foci. The mother was very dissatisfied, and after further consultation the girl was admitted to Royal Prince Alfred Hospital. Here a bronchoscopy revealed the piece of rubber in a branch of the left bronchus. The rubber was removed, and thereupon both the cough and the chest signs cleared up. The girl has had no recurrence of the trouble.

Case II.

Jack —, aged three years, was brought to me on June 6, 1930, with the following history. During the afternoon he had been playing with some 0·22 short cartridge shells, when he developed a sudden attack of coughing with severe dyspnœa. The mother recovered two shells from his throat with her finger and felt another beyond her reach.

When examined, the child's breathing was audible and croupous, and at each expiration a definite click could be heard. Nothing could be seen above the vocal cords. The child was at once sent to Sydney for bronchoscopic examination and the cartridge shell was recovered.

Case III.

Joyce —, aged eighteen months, was brought in on November 19, 1930, with the history of having developed a croupy cough with loss of voice during the previous afternoon. The mother stated that the infant had been playing on the floor, upon which a number of dead leaves were scattered, and that she had taken from the child a piece of leaf.

When examined, her temperature was 37·5° C. (99·6° F.), pulse 120. There were both inspiratory and expiratory stridor, and her cry was soundless. She was admitted to hospital with a provisional diagnosis of laryngeal diphtheria. Sixteen thousand units of diphtheria antitoxin were given, and the child placed in a steam tent. The following day a further 10,000 units were given, as the stridor and recession were still present. The temperature was normal. On the third day another 6,000 units were given. On the fourth day the temperature rose to 38·9° C. (102° F.) and the child collapsed. Hourly stimulants of strychnine and digitalin were given, and definite signs of pneumonia appeared in the right upper lobe of the lung. The temperature remained between 38·3° and 39·4° C. (101° and 103° F.) for twelve days and then gradually dropped to normal. During this period the attacks of stridor were less severe, though recession was still present. On December 9 the child was sent to Sydney for bronchoscopic examination and was admitted to Royal Prince Alfred Hospital.

There she was examined by X rays (no evidence of foreign body being found), but the bronchoscopic examination was not made. Three days later she was discharged. Acting on medical advice, the parents took the child to the

country. The attacks of stridor continued, and during one attack a modified intubation was performed by the father with a rubber tube, which appeared to give temporary relief.

On February 4, 1931, the attacks still persisting, I advised the parents to take the child again to Sydney for bronchoscopic examination. Dr. C. G. McDonald was this time consulted, and at his request the bronchoscopic examination was made. No foreign body was located. The following day the child's condition became worse and physical examination revealed pneumonia of the left upper lobe. Death occurred early the next morning, the sixtieth day of the illness.

Post Mortem Report.

The left lung showed patchy consolidation and the two lobes were adherent. In the main bronchus, about 2·5 centimetres (one inch) from the bifurcation of the trachea, a piece of gum leaf was found.

Comment.

In each case the previous health of the child had been normal. There was a noticeable similarity in the type of breath sounds; Osler describes it as an "asthmatoid wheeze."[1] X ray examinations in Cases I and III revealed no abnormality of the lungs; Case II was so obvious that X ray examination was deemed unnecessary. In each case the patient's story was of overwhelming importance; the mode of onset and the subsequent symptoms pointed strongly to the advisability of bronchoscopic examination.

Acknowledgement.

I am indebted to Dr. C. G. McDonald for his notes on the clinical condition and *post mortem* findings of the third patient mentioned.

Reference.

[1] Osler's "Modern Medicine," Volume IV, 1927.

RUPTURED HYDATID CYST OF SPLEEN.

By A. CALLOSE, B.Sc., M.B., B.S.,
Resident Medical Officer, Western Suburbs Hospital, Croydon, New South Wales.

C.W., AGED thirty-six, a hairdresser, was brought to hospital one night at 10.45 p.m., complaining of very severe pain over the whole abdomen. He gave a history of having been boxing early in the night, and following a quick turn to avoid a punch, he was seized with severe abdominal pain which shot down to both testicles.

On arrival at the hospital the pain had not eased and he was rolling about in great pain. He had not vomited nor was he nauseated. He had voided urine without difficulty shortly after onset of pain.

For the past four to five years he had complained of epigastric pain and flatulence with occasional vomiting. He was losing weight.

On examination his colour was good, his pulse rate 68. Its volume was good. His temperature was 37° C. (98·6° F.). His respirations numbered 28 in the minute. The tongue was clean and moist. Both legs were held fully extended, as flexion increased severity of the pain. Board-like rigidity of the whole abdomen was present. Tenderness was pronounced, especially in the epigastrium. No mass was palpable. No dulness was present. All other systems were clear. He voided urine shortly after admission. The urine was acid and clear; its specific gravity was 1·024.

The next morning he was still in great pain, which had now settled in the upper part of the abdomen. There was board-like rigidity of the upper half, with a slight distension of the lower half. He had not vomited. His pulse rate was 70; his temperature was normal. Respirations numbered 26 in the minute. At midday his condition was unaltered, except for a little dulness in the left iliac region. The pulse rate, charted every half hour since admission, varied between 60 and 70.

On account of the persistent rigidity, it was thought advisable that an exploratory operation be performed. This was done by Dr. Eric Fisher, Honorary Consulting Surgeon, at 2 p.m. Under the anæsthetic a fluid thrill was obtained over the lower part of the abdomen. On opening the peritoneal cavity a quantity of free blood and blood clots was found. Stomach and duodenum were normal. The spleen was then palpated. Some blood clots were found around it; on removing them, the finger could be passed into a cavity. This was thought to be a rupture in the spleen, but on withdrawing the hand, thin, white, membranous substance was found. On closer examination this was found to be degenerated hydatid daughter cysts. The cyst was central and about half of the whole organ was replaced by the parasite. The rupture had caused hæmorrhage from the splenic pedicle into the peritoneal cavity and also into the lesser sac. The spleen was bound to the diaphragm by a few bands of adhesions. Splenectomy was performed.

On further exploration several small cysts, each about the size of a hen's egg, were found along the inferior border of the liver. All cysts appeared to be primary. No secondary cysts were found in the peritoneal cavity. The hepatic cysts were not treated, as the patient's condition did not warrant any prolonged operation.

He made an uneventful recovery. Later he will undergo a further operation for the hepatic cysts.

The residential history was that he was born at Bredbo, New South Wales, where he lived for five years. Then he lived at Homebush, New South Wales, for ten to eleven years. As a schoolboy he often visited the slaughter yards. He is now living at Concord. A dog was always kept at home.

Comment.

Hydatid disease of the spleen is comparatively rare. No definite figures are available for Australia, but from Dew's[1] observations, the incidence is the same as that in other countries. Thomas gives 2%, Dévé 2·1%, Greenway 2·3%. Considering these figures, the rarity of a ruptured cyst of the spleen must be further emphasized.

Reference.

[1] H. R. Dew: "Hydatid Disease," 1928, Chapter XVII, page 280.

GAS GANGRENE OF THE UTERUS FOLLOWING FAILED FORCEPS.

By T. DIXON HUGHES, M.B., Ch.M.,
Honorary Assistant Surgeon, Women's Hospital, Crown Street, Sydney.

MRS. X., aged thirty-seven years, a *primipara*, was admitted at 4 p.m. on September 14, 1930, with a temperature of 37·2° C. (99° F.) and a pulse rate of 100. She had a history of having pains for two days. An attempt at delivery with forceps had been made that afternoon before admission. On examination the general condition of the patient was good. The fœtus was in the left occipito-anterior position. The head was not in the pelvis, there was no overlap, the fœtal heart could not be heard. The vagina was extremely lacerated, the cervix was thick, œdematous and lacerated, only half dilated and not taken up. The patient was given 0·015 gramme (a quarter of a grain) of morphine and chloroform inhalation. She had a sleep and at 9 p.m. the cervix was commencing to thin out. More morphine and chloroform were given. The patient slept well, but her temperature went up to 39·4° C. (103° F.) and the pulse rate was 130 at 2 a.m., and then it commenced to steady. At 10 a.m. the temperature was 37·4° C. (99·4° F.) and the pulse rate 100. The patient's general condition was good. She requested toast and eggs for breakfast. A consultation was held with Dr. Donovan at 10 a.m. and he concurred with the view that, as the head had now entered the pelvis and descent was taking place, as little manipulative interference as possible should be undertaken in view of the lacerations to vagina and cervix. At 12.30 pains were regular, but of poor tone,

0·18 ml (three minims) of pituitrin was given and this was repeated at 1.10 p.m. At 1.50 the pains ceased and the patient complained that something had snapped. A condition of collapse rapidly set in. The pulse was thin and feeble, respirations were rapid and cyanosis and sweating were present. The abdomen appeared to be increasing in size and no fœtal parts could be felt owing to the tenseness of the abdomen. She was hurried to the theatre and operated on by Dr. Donovan, on opening the peritoneum, which was extremely tense, a loud report was heard as a quantity of foul gas escaped, and on opening the uterus an even louder report was heard. After extraction of the fœtus the uterus collapsed like a wet rag and had the typical greyish colour and wash-leather feel; it showed no tendency to bleed. A rapid hysterectomy was performed, a drain was put into the pouch of Douglas, the cervical stump was stitched to the wound so as to marsupialize it. Antigangrene serum was given. The patient, although rallying for some time, died five hours later. The uterus had been placed in a dish of preservative in which it remained for an hour, when it was removed and a section of muscle was cut from the inside; from this a culture of *Bacillus welchii* was grown.

The points of interest are:

1. The dangers of high forceps on an unmoulded head.
2. The dramatic suddenness of onset.
3. The presence of all the desiderata for this type of infection: (*a*) Dead fœtus, (*b*) laceration of vagina and the anaerobic condition present at the site of deep lacerations of the cervix, (*c*) interference from without.

Reviews.

PROGRESS IN GENERAL MEDICINE.

THE "General Medicine" volume of the "Practical Medicine Series," 1930, makes interesting reading.[1]

The usual alphabetical arrangements of subjects in a yearly review is displaced by a division of the volume into four departments: infectious diseases, diseases of the chest (excepting the heart), diseases of the blood and blood making organs, including diseases of the kidney, diseases of the heart and blood vessels, diseases of the digestive system and metabolism.

This division into departments makes for greater continuity of subject and easier reading. Each department, with the exception of that dealing with infectious diseases, is controlled by one editor, whose hand can be seen not infrequently in short paragraphs emphasizing a point made or issuing a warning note against the too ready acceptance of views quoted. Every reader will find much to criticize, but the book should be accepted as being, as it is intended to be, a compilation of views of other workers. Articles do not appear to be too drastically curtailed, whilst some of the more important are reviewed at length. The literature is extensive and whilst American references are numerous, English, Continental and Australian articles will be found amongst them.

In mentioning some of the more interesting subjects noted, we might draw attention to the use of insulin and dextrose in the treatment of circulatory failure in the early stages of diphtheria, the details and the criticism of the Gerson *régime* and diet in the treatment of pulmonary tuberculosis, the very full review of the literature published during the year on liver therapy and its effects upon the anæmias and the nomenclature for cardiac diagnosis adopted by the American Heart Association. Lipoid nephrosis is discussed from several angles and one article devoted to renal tuberculosis is well written. The pages devoted to arteriosclerosis and also those devoted to the clinical aspect and treatment of coronary thrombosis will repay the time spent in reading them. A short article on the results of medical treatment of gastric ulcer in over one thousand cases reported by Sippy and Brown gives cause for thought, as does another article on the X ray diagnosis of gastric carcinoma. An article by Bram, giving the differential diagnosis between toxic adenoma and exophthalmic goitre and his views on treatment, leaves room for controversy.

A commendable feature of the volume is the space devoted to treatment. This alone makes the volume a useful addition to the physician's library.

[1] "Practical Medicine Series: General Medicine"; Series 1930. Chicago: The Year Book Publishers. Crown 8vo., pp. 848. Price: $3.00 net.

FORENSIC MEDICINE.

THE latest addition to the "Recent Advances Series" is a volume dealing with forensic medicine, by Sydney Smith and John Glaister.[1] The book is of great interest and contains much information that is not readily accessible to the majority of medical readers. The first chapter on the diagnosis of injuries from projectiles will be useful to all medical practitioners who are called upon to investigate gunshot wounds. Country medical practitioners, holding the position of government medical officers, will find this chapter indispensable. The chapter on the medico-legal examination of hairs will perhaps not have such a wide appeal, since hairs can be readily sent to an expert for examination. The precipitin reaction and the application of the precipitin test receive considerable space. The technique of the test is given in detail and other medico-legal tests based on the action of precipitins are discussed. Blood grouping and inheritance, and spectroscopy in medico-legal work are considered. In the chapter on the estimation of alcohol in blood and urine the authors express the opinion that, though the test can prove that a definite quantity of alcohol has been taken, it cannot be relied upon as a test of alcoholic intoxication.

This book covers much important ground. For the introduction of new work a lot that is not new has had to be mentioned. All medical practitioners concerned in any way with medico-legal work will do well to study this volume.

[1] "Recent Advances in Forensic Medicine," by Sydney Smith, M.D., M.R.C.P., D.P.H., and John Glaister, M.D., D.Sc.; 1931. London: J. and A. Churchill. Post 8vo., pp. 200, with 66 illustrations. Price: 12s. 6d. net.

SKIN GRAFTING.

MR. KENRICK CHRISTIE, in his small book, "Technique and Results of Skin Grafting," describes the methods he has used in treating a series of patients, mostly suffering from chronic ulcers of the leg.[2] He states that there is an occasion for each type of graft, Thiersch, Wolfe and the tube pedicle graft, but in his hands the Wolfe graft has the widest application.

The success he has had with large Wolfe grafts upsets many text book teachings, as he has successful results with whole skin grafts up to forty square inches in extent. This success he attributes to extensive excision of all scar tissue at the base of the ulcer, accurate apposition of the graft, the absence of buried suture material, operating on the exsanguinated limb, and firm pressure preventing elevation of the graft with effusion of blood; this pressure he maintains with Stent mould.

His methods are clearly described and his case records, illustrated by excellent photographs, occupy a large portion of the book. The photographs show the graft to be healthy up to two years after its application, but records longer than these could not be obtained. The author preserves a strange silence regarding the undoubted usefulness of the various forms of pressure treatment of chronic ulcers and also of injection therapy of the so often concomitant varicose veins, but if this small book stimulates its readers to more adequate treatment of those long suffering patients so often relegated to the back waters of the surgical out-patient department, it will have served its purpose. The book should be of value to all interested in skin grafting and a lesson to many.

[2] "Technique and Results of Grafting Skin," by H. K. Christie, M.S., F.R.C.S.; 1930. London: H. K. Lewis and Company Limited; Sydney: Angus and Robertson. Demy 8vo., pp. 79, with 35 illustrations.

The Medical Journal of Australia

SATURDAY, JULY 11, 1931.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction, are invited to seek the advice of the Editor.

THE PRACTICE OF PHYSICAL THERAPY.

IN a recent issue of *The British Medical Journal* there appeared an account of a proposal to form a "group" within the British Medical Association of members engaged in the study and practice of electrotherapeutics and physiotherapeutics. The proposal took the form of a petition to the Council; it was signed by forty-two members. The discussion in Council was most interesting and although it was finally decided that the Council should accede to the formation of the group, several well-known councillors spoke in opposition to the proposal. In Great Britain the Council has power to form "special groups" of members who have distinctive professional interests and who, by reason of their paucity of numbers or of their local distribution, are unable to obtain adequate representation of those interests through the Divisions and Branches. A group may not be formed unless it is shown that the ordinary machinery of the Association is not sufficient for such representation. When the Council authorizes the formation of a group, it defines the class of members who shall be included in the group, and every member of the Association coming within the Council's definition is *ipso facto* a member of the group. Sir Robert Woods said that those concerned had come to the British Medical Association because the Section of Physical Medicine of the Royal Society of Medicine, to which they belonged, was precluded from dealing with any but purely scientific matters. From these happenings it is obvious that medical practitioners in Great Britain are concerned about the activities of those people who endeavour to "thrust their way into those bypaths of medical practice" and who use physical therapy in a way that is not likely to benefit the patient nor to redound to the credit of the agency used.

In recent years physical methods of therapy have found a definite and important place in the armamentarium of surgeon, physician and specialist. The methods are of wide application and include those of heliotherapy, electrotherapy, radiotherapy, hydrotherapy, massage, exercise and so on. None of these means of treatment should be used in a haphazard fashion; the more they are studied, the clearer it will become that each has its sphere of usefulness and that the limitations are oft-times very narrow. The ease with which many of these forms of therapy can be applied makes their exploitation by non-medical persons a simple matter. A great deal might be written about this aspect of physical therapy, evidence of actual harm done to sufferers from disease might be adduced, tales of exploitation of both rich and poor might be told, and a good case might be made out for the restriction of the use of all forms of physical therapy to persons who have undergone a medical training, or to persons who have studied a particular method of therapy and act only under the direction of a medical practitioner. But exploitation does not always come from outside the medical profession; there is a great deal of quackery within its ranks. The diathermy machine, the X ray examination equipment, the mercury vapour lamp and other appliances are often used merely to impress the patient. Sometimes the medical practitioner unconsciously deceives himself and mistakes the *post hoc* for the *propter hoc*; nothing is simpler. Self-deception of this kind is a danger that faces all medical practitioners. Authors of books on physical therapy are often responsible for false beliefs. If some of them are to be believed, there is

scarcely a single condition among the ills of mankind in which ultra-violet light or diathermy is not indicated. Here massage may be mentioned. There is a great deal to be said for a recent statement of Dr. C. E. Corlette that much of the massage given after trauma is useless and is not treatment at all. The medical profession in Australia is not alone in having to deal with these internal problems of physical therapy—the problems as they affect those who profess belief in the efficacy of physical therapy.

Physical therapists in Australia have to see to it that discredit is not brought on the methods that they use. They cannot form a "group" within the British Medical Association similar to that being formed in England. If a section of a Branch in Australia is formed for the study of any aspect of medical science, there is nothing to prevent any member of the Branch from joining the section. Though the disadvantage is obvious, it must be remembered that medical practitioners who are ignorant or have but a little knowledge of physical therapy, will learn a proper perspective, if nothing else, by belonging to such a section. The formation of a separate society would be useless; medico-politically, it would lack the weight of a section of the British Medical Association. The advisability of establishing a diploma in physical therapy has been suggested. It might be useful. These points need consideration. But before the medical profession as a whole adopts any "hands-off" policy to non-medical persons, it must purge its own ranks and the avowed physical therapists must go through a course of introspection. There must be no misrepresentation and no humbug.

Current Comment.

ULCERATIVE COLITIS.

AUTHORITATIVE opinions concerning the causation and treatment of ulcerative colitis are so many and varied that the medical practitioner seeking to learn something of this condition is apt to become bewildered. He can, however, seek comfort in the reflexion that the most learned authority is unable either to assign a cause to ulcerative colitis or to prescribe a method of specific therapy. Treatment at spas and the administration by mouth and by anus of innumerable so-called intestinal antiseptics have been advised; pharmacopœial drugs and scores of drugs with fantastic names, doubtful origin and more dubious effect have been experimented with and recommended and used the world over; vaccines and antisera have both been given with an apparent success which has varied with different observers; caecostomy, appendicostomy, ileostomy and ileo-sigmoidostomy are the surgeon's contribution. Surgical treatment is worthy of special mention. At first glance it would appear that in surgery is the solution of the problem of treatment, for the colon is given rest and a means of applying a *vis a tergo* in the matter of colonic lavage is provided. But the operation most commonly performed—appendicostomy—does not provide a means of resting the colon, and it has yet to be proved that the colon can be more efficiently washed out from above than from below. Surgery has been at once the cause of many disasters and the means of saving many lives. It is of the greatest value when applied at the appropriate time; it should be neither despised nor unduly relied upon, but should be availed of when the occasion requires it.

At a meeting of the Section of Surgery, Subsection of Proctology, of the Royal Society of Medicine in March of this year, ulcerative colitis was discussed by a number of authorities, of whom Arthur F. Hurst as physician, P. J. Briggs as radiologist, Cuthbert Dukes as pathologist, and J. P. Lockhart-Mummery as surgeon introduced the subject from their various points of view.[1]

Hurst believes that ulcerative colitis is really a form of bacillary dysentery; he remarks on the difficulty of isolating the *Bacillus dysenteriæ* after the acute stage of dysentery has passed. He advocates the administration of antidysenteric serum and claims to have had good results with this method of treatment. He recommends "rest in bed, warmth and a generous mixed diet, from which the skins and pips of fruit and fibres of vegetables are alone excluded." He remarks on the value of blood transfusion, not only in its effect on the anæmia, but also its beneficial influence on the ulcers themselves. He advises local irrigation with tannic acid solution (one in one-thousand) after lavage with normal saline solution. Hurst is a staunch advocate of proctoscopic or sigmoidoscopic examination of every patient; he draws attention to the likelihood of confusion between ulcerative colitis and amœbic dysentery and ulcerative colitis and carcinoma; he stresses the fact that such confusion cannot exist if the sigmoidoscope be used. He quotes one remarkable instance of a man who was supposed to be suffering from ulcerative colitis of long standing; sigmoidoscopic examination revealed that the blood was coming from hæmorrhoids and that the rectum, the mucosa of which was quite normal, contained effervescent fluid fæces, the result of carbohydrate intestinal dyspepsia.

Dukes remarks that the ulceration is often most pronounced "opposite to the longitudinal muscle

[1] *Proceedings of the Royal Society of Medicine*, April, 1931.

bands of the colon, between which is seen a thin strip of irregular fringed surviving mucous membrane." Stricture occurs as a sequel in 8·5% of cases and perforation in 2·6%. If healing occurs the ragged polypoidal tags of mucosa which often remain, are much less likely to become carcinomatous than are true adenomata or polypi. Dukes discounts the several theories of specific causation of ulcerative colitis and suggests that the condition occurs in intestines which are congenitally inferior and which are unusually susceptible to trauma and bacterial invasion. He recommends the employment of autogenous vaccines only when the patient's serum agglutinates bacteria from the ulcers.

Lockhart-Mummery states definitely that in the majority of cases ulcerative colitis is due to infection with streptococci, but he remarks also that tubercle bacilli, pneumococci and occasionally other organisms are found as the primary infecting agents. If the disease be mild, non-operative measures may suffice to effect a cure, but appendicostomy is the method of choice and is curative provided it be performed sufficiently early. He stresses the value of appendicostomy from an economic standpoint, remarking that many patients are unable to afford the handicap of having to lie up, often for months, in order to receive medical treatment during their periods of relapse. Lockhart-Mummery also regards the use of the sigmoidoscope as a necessary aid to diagnosis and a means of ascertaining progress.

H. Letheby Tidy, who took part in the discussion, believes that neither sigmoidoscopy nor operation is necessary.

In opposition to Dukes, L. P. Garrod regards Bargen's coccus, which has been found capable of causing lesions in the rabbit's bowel, as of ætiological significance. The organism was discussed in these pages on July 26, 1930, in the light of some work by Bargen. Diathermy and ionization in treatment are mentioned by others, and almost all bring forward their own ideas with regard to medication, and these are of great variety. The situation with regard to treatment is well summed up by F. J. Poynton when he states that treatment seems to be a matter of individual experience and that the physician obtains his best results with medicines, the surgeon with surgery, the specialist with bowel washing and other methods.

All this disagreement means that little is actually known concerning the ætiology and treatment of the disease. Avitaminosis and metabolic disturbances cannot be discarded as possible contributing causes of the condition; perhaps in many instances either one or both of them may have some considerable influence. But there seems to be no valid reason why the theory of specificity should be discredited; there are other known specific ulcerations of the intestinal tract, each of which has distinguishing pathological features. Ulcerative colitis presents definite clinical and pathological pictures, only its cause remains in doubt. The cause or causes will eventually be found; in the meantime, in the absence of a specific cure, each medical practitioner, while never neglecting certain general principles, should continue to apply the treatment which he finds gives him the best results.

POST-VACCINAL ENCEPHALITIS.

THE manner in which one virus infection may act on another has not been determined. It has been supposed that infection with a virus of one type may call into activity a latent affection due to another or that it may modify the lesions produced by another. These possibilities are of considerable clinical importance and it is therefore of interest to note a recent investigation by E. W. Hurst and R. W. Fairbrother.[1] They experimented on monkeys with the viruses of poliomyelitis and vaccinia and gave both intracerebral and intradermal inoculations. The details of the experiments are immaterial, but it should be noted that they conclude that infection with a highly virulent vaccine virus, a neurovaccine, has no power to modify the nervous lesions of poliomyelitis; this was found to be equally true whether the vaccine was injected directly into the brain or into the skin. If both viruses were given intravenously, the resulting vaccinal reaction did not suffice to break down the hæmato-encephalitic barrier and permit invasion of the nervous system by the poliomyelitis virus. Hurst and Fairbrother were not able to demonstrate an activation effect of vaccinia on a weak poliomyelitis virus.

These findings are admittedly of a negative or inconclusive nature, and Hurst and Fairbrother point out that in applying them to the problem of post-exanthematous encephalomyelitis, it must be remembered that much other evidence is opposed to a participation of the poliomyelitis virus in its causation. They are commendably cautious in their final conclusion when they state that while it is unsafe to generalize from experience with one neurotropic virus only, their findings make it unlikely that, if post-vaccinal encephalitis is due to the activation of a latent neurotropic virus by vaccination, any virus hitherto isolated and studied is responsible for the nervous disease.

MEDICAL EXAMINATION OF UNIVERSITY STUDENTS.

AN important innovation is about to be introduced at the University of Sydney. The Senate, at the instance of the Advisory Council of the School of Public Health and Tropical Medicine, has agreed to the introduction of health supervision on a voluntary basis. The test will be designed to reveal defects likely to interfere with progress in studies or with health and physical fitness. A personal report will be made to the student; general statistics only will be submitted to the Senate. This examination should be encouraged.

[1] *The British Journal of Experimental Pathology*, February, 1931.

Abstracts from Current Medical Literature.

MORBID ANATOMY.

Mixed Tumours of the Salivary Glands.

ERHARD KUX (*Virchow's Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, February 4, 1931) writes on the histogenesis of mixed tumours of the salivary glands. He points out that these tumours have three possible modes of origin: (i) a connective tissue, endothelial origin, (ii) an epithelial origin, (iii) a combination of both these. He discusses the histological appearances in detail and describes minutely the "*Schichtungskörper*" or layer bodies. These are masses of cells arranged concentrically. Their structure is not always uniform. In many places they consist of more or less numerous layers of cells arranged like the layers of an onion around a middle point; these may have no nuclei and may be the site of calcareous change. Often in the middle there lie cell remains, leucocytes or calcareous granules. In place of the ring-like formations there may be quite homogeneous structureless masses. The "*Schichtungskörper*" or layer bodies may be of epithelial or endothelial origin. In their epithelial descent they may be derived on the one hand from embryonic epithelial and gland epithelial cells which become differentiated into squamous epithelium; on the other hand, they may arise from the gland cells themselves. Such structures may be formed from the epithelial glandular cells as a result of the damming up of glandular secretion. The author states that the lack of epidermoidal cell constituents does not exclude the epithelial origin of the concentric bodies. As far as their endothelial origin is concerned, they may arise from vessels which have undergone hyaline degeneration. The cartilaginous nature of the supporting tissue can be proved morphologically and also histochemically. The author concludes that there is evidence that the tumours are built up from two embryonic layers and that use of the term mixed tumours is justified.

Pseudotuberculosis and Hæmochromatosis.

WALTER UMLAUFT (*Virchow's Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, February 4, 1931) reports two cases of pseudotuberculosis in man; he states that five have been previously reported in the literature. The pseudotuberculosis of man is a definite and characteristic disease which presents a clinical picture similar to that of typhus fever. It can easily be differentiated from the latter. From the pathological and anatomical points of view it is characterized by definitely recognizable granulation tissue in the liver, spleen and portal lymphatic glands and by its association with a general hæmochromatosis. The hæmochromatosis is the primary disease. The pseudotubercle bacilli produce a specific virulent toxin which acts on the reticulo-endothelium of the liver, spleen and portal lymphatic glands. Under normal conditions the toxin will be rendered innocuous by the reticulo-endothelial system. Only when specific injury of the reticulo-endothelial system has occurred, as in hæmochromatosis, can the pseudotubercle bacilli pass from the blood or lymph stream into the tissue of the organs and there produce a nodular formation.

Pseudotuberculosis and Tularæmia.

H. A. REIMANN AND W. J. ROSE (*Archives of Pathology*, April, 1931) write on the similarity of pseudotuberculosis and tularæmia. The striking similarity of the clinical histories and of pathological reports of the two conditions suggests the possibility of a relationship between them. Experiments on animals with *Bacillus pseudotuberculosis* yield for the most part results similar to those obtained with *Bacillus tularensis*. The same animals are susceptible and similar lesions are found on macroscopical and microscopical examination. The absence of typical giant cells in the nodules of both diseases is of particular interest. Final proof of the relationship can be obtained only by bacteriological and serological study.

Diffuse Meningeal Carcinomatosis.

HELENE SCHUSTER (*Virchow's Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, February 4, 1931) reports a case of diffuse meningeal carcinomatosis. He points out that the condition is rare and that it is reported by different authors as lympho-endothelioma, endothelioma, perithelioma or carcinoma, because the origin has not been definitely determined. The author's patient was a woman, fifty-seven years of age. At the time of death the clinical diagnosis was tumour of the brain in the region of the base of the skull. At the *post mortem* examination the *dura mater* was found to be thickened. Clear, somewhat turbid fluid was found in the cranial cavity. The *pia mater* was thickened and whitish. This appearance was partly diffuse, partly in aggregated masses and in places nodular, particularly along the course of the blood vessels. The ventricles were distended and contained turbid fluid. The lungs were the seat of extensive tuberculous change. From the autopsy findings it was concluded that the cause of death was general cachexia and anæmia caused by tuberculosis of the lungs and glands and by chronic inflammation of the meninges. When the latter were subjected to microscopical examination the findings were quite unexpected. The *pia mater* was thickened. In the *pia mater* and in the connective tissue spaces there were regular tumour cells in rows and masses resembling glandular cells. They were arranged round the spaces so that they gave the impression of adenocarcinoma. The cells were large and of varying shapes, mostly cylindrical, some were cubical, some round and others heterogeneous. Many cells were binuclear or polynuclear. Degenerative changes were seen in the cells. The cells lay apparently free near one another in a single layer; they sometimes gave the impression of being disconnected. In places the cells penetrated the cortex and were either arranged in a single layer or in radiating masses round the vessels. In the cerebellum the infiltration was so pronounced that the membranes could not be distinguished from the cortex. The growth originated in the chorioidal plexus. The author points out that in similar cases it has not been possible to determine the origin of the growth. He also emphasizes the fact that the growth could not be seen with the naked eye.

The Mucosa of the Stomach in Ulcer and Cancer.

HORST PUCHERT (*Virchow's Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*, March, 1931) has investigated the mucosa of the stomach in gastric ulcer and gastric carcinoma. He finds that the gastritis accompanying ulcer is confined to the antrum and that in the fundus only a condition of irritation is found. The gastritis is subacute, but there is also present a moderate degree of chronic inflammatory change. The lymph follicles are markedly increased in number and in size by the appearance of secondary follicles. Bowel epithelial metaplasia, if it occurs at all, is found only in small patches. The gastritis in primary cancer is a generalized gastritis (pangastritis) and is always of the so-called chronic variety, though slight acute exacerbations occur. The follicles are mostly increased in number and small, and show definite degenerative changes, such as hyalinization and atrophy. Goblet cell metaplasia is to be found in large areas. In regard to secondary cancer no general conclusions were possible. As a rule inflammation occurs only in the neighbourhood of the tumour. The author's negative bacteriological investigations lead him to suppose that it is the toxic products of disintegration of the ulcer and cancer which aggravate an existing gastritis. The state of the lymphatic tissue points to a further toxic action.

Giant Cell Tumour of Bone.

S. C. DYKE (*The Journal of Pathology and Bacteriology*, March, 1931) states that there is a tendency to regard as essentially benign and incapable of metastasis the bone tumour known as myeloid sarcoma, osteoclastoma and benign giant cell tumour of bone. He reports a case which in his opinion demands a revision of this view. The patient, a male, twenty-five years of age, suffered from a swelling of the patella which was curetted. Examination of

curettings resulted in a diagnosis of "giant-cell tumour of bone." For more than three years no trouble was experienced, but then the patient injured the knee, which became swollen and hæmorrhagic. Subsequently the limb was disarticulated at the hip joint. Death occurred about six years after the appearance of the first symptoms. Metastases having the same structure as the original growth were found in the scalp, lungs, kidneys and mediastinal and peritoneal lymphatic glands. The author refers to similar cases reported by other observers. He concludes that unless it is completely eradicated, the tumour is liable in the course of time to assume malignancy of a high order.

Experimental Bone Sarcoma After Radium Irradiation.

O. SCHÜRCH AND E. UEHLINGER (*Zeitschrift für Krebsforschung*, March, 1931) inserted a radium needle containing one milligramme of radium into the periosteum of both angles of the jaw of a rabbit. No changes were observed on the left side, but the right jaw angle, which was irradiated with 480 milligramme-hours, developed a swelling a year and a half after irradiation. The swelling appeared exactly where the irradiation took place. The swelling increased in size rapidly till it reached the size of a mandarin orange. Then the animal was killed. On X ray examination the swelling was recognized as mainly an osteolytic tumour of the right mandibula. On histological examination the tumour was found to be an osteogenetic sarcoma with distinct signs of malignancy. The growth was not considered to be a giant-cell tumour.

MORPHOLOGY.

Attempts to Promote the Reformation of Germ Cells.

MARGARET HILL AND A. S. PARKES (*Journal of Anatomy*, January, 1931) found that the administration of preparations containing the gonad-stimulating principle of the anterior pituitary body does not increase the percentage of ovarian regeneration in mice whose ovaries have been removed, or cause the reformation of oöcytes in mice sterilized by exposure to X rays.

Union of Epihyses.

FROM the results obtained and classified in a series of tables Girgis, Lidhom and Derry (*Journal of Anatomy*, January, 1931) believe they have evidence that Egyptian males are definitely earlier than English in the union of some at least of the epiphyses of the upper limb. The results also seem to illustrate the unreliablity of the findings obtained at times from X ray photographs. To lessen this source of error they have instituted a method of classification by stages, based on the known mode of ossification of the ends of long bones. They divide the whole process into three stages. In Stage I the cartilage occupies the interval between the epiphysis and diaphysis and in the photograph the separation of the two is easily seen. In Stage II the plate of bone representing the fusion of the diaphyseal and epiphyseal plates is conspicuous and can be seen in the photograph as a dark line. Stage III is reached when the bony plate is entirely absorbed and replaced by spongy bone. This may take months or even years.

The Innervation of the Ocular Muscles.

H. H. WOOLLARD (*Journal of Anatomy*, January, 1931) gives an account of an investigation on the innervation of extrinsic eye muscles. He finds that there are two types of nerve fibre concerned in the innervation of the eye muscles, the ordinary medullated type with motor terminal plates, and a second, finely medullated or non-medullated, forming several claw-like endings, usually epilemmal, but occasionally hypolemmal. The medullated fibres are related to thick muscle fibres, while the non-medullated are related to thinner muscle fibres. It was not observed that the thinner muscle fibres also receive a medullated ending. Evidence was obtained that the non-medullated fibres have their origin in the cranial extension of the *tractus mesencephalicus* of the fifth nerve where this is on a level with the third nerve nucleus, and so are probably sensory.

The Growth of the Brain of the Australian Aboriginal.

H. H. WOOLLARD (*Journal of Anatomy*, January, 1931) finds that the brain of the Australian aboriginal fœtus in its general conformation resembles the fœtal brain of the white. The extreme dolichocephaly of the adult is due to later unequal rates of growth. The dimensions of the cortical fissures in the principal areas of the adult brain indicate that absolutely and relatively the occipital area is the most developed; that the parietal and frontal areas are moderately developed, the frontal, however, falling behind that of the white; while the temporal area lags very far behind that of the white. The histological examination of the cortex shows that the degree of cell stratification is less well established than in the white brain, except in the visual areas. Everywhere the cerebral cortex is thinner than in that of the white brain, and the number of cells is both absolutely and relatively fewer.

Total Thyreoidectomy and the Pituitary Gland of the Rabbit.

A. R. BRYANT (*Anatomical Record*, November, 1930) states that complete removal of the thyreoid gland in the rabbit results in an enlargement of the pituitary body. This increase in size is exclusively in the anterior lobe, and is due to a progressive hypertrophy of the chromophobe cells. There is also a progressive reduction in the number of the eosinophile cells. Also many of the hypertrophied chromophobe cells degenerate, first becoming vacuolated and then completely breaking down, leaving large gaps containing cellular *débris*. These results are not interpreted as indicating an increased secretory activity of the pituitary gland in cases of thyreoid deficiency, but may be due to a depression of the specific secretion of the cells affected. The profound modification of both α cells and chromophobes suggests that some of the results of thyreoid deficiency may be produced indirectly through depression of the pituitary gland.

Some Effects of Œstrin on Baboons and Macaques.

A. S. PARKES AND S. TUCKERMAN (*Journal of Anatomy*, January, 1931) find that ovariectomy causes immediate atrophy of the sexual skin of the baboon and cessation of flow of mucus in the bonnet monkey. Injection of œstrin after ovariectomy causes the appearance in the baboon of a swelling precisely similar to that found in the normal animal during the follicular phase and a return of mucous flow in the bonnet monkey. Injection of œstrin after gonadectomy has no effect on the sexual skin of the bonnet monkey or on the pudendal skin of the male rhesus, and very little effect on the mammary glands of the baboon, the bonnet monkey or male rhesus monkey.

The Structure of the Renal Corpuscle.

R. R. AND R. D. BENSLEY (*The Anatomical Record*, November, 1930) give an account of an investigation on the structure of the renal corpuscle, using new methods of staining. They conclude that the glomerular epithelium is a continuous layer over the whole extent of the surface of the glomerulus and its lobes, that the glomerular epithelium is composed of separate cells and does not constitute a syncytium and that the endothelium of the glomerular capillaries is continuous, without defects. In some human kidneys the capsule of Bowman consists of the layers: capsular epithelium, structureless basement membrane, and an outer layer of reticulum. In others the structureless basement membrane was not demonstrable in the capsule.

The Vascular Supply of the Archicortex of the Rat.

E. HORNE CRAIGIE (*Journal of Comparative Neurology*, October 15, 1930) gives an account of studies of the vascularity of the archicortex and compares it with that of the neocortex. In both *fascia dentata* and *hippocampus* proper the molecular layer was markedly the richest in vascularity, surpassing also the corresponding layer in all parts of the neocortex which were examined. The other laminæ are poor as compared with the neocortex. In a general way the archicortex ranks in capillary richness with the poorest of the sensory and correlation regions.

Special Articles on Diagnosis.

(Contributed by Request.)

LII.

INFECTIONS OF THE CONJUNCTIVA.

THE classical symptoms upon which a diagnosis of conjunctivitis is made—inflamed and swollen lids accompanied by hot, burning sensations, with a feeling as if sand were in the eyes, heaviness of the lids, with the addition of momentary clouding of the vision and sticking of the lids from the consequent secretion, but without any great amount of photophobia or pain in the eye (these latter occurring only when corneal or iritic complications are present)—are far too well known to need emphasizing. The purpose of this paper will be to draw attention to the salient features and mistakes that can be so easily made, and so assist the general practitioner, who is more often called upon to treat the condition than the specialist, excepting in those cases which do not for some reason respond to treatment.

Catarrhal Conjunctivitis.

In acute catarrhal conjunctivitis both eyes are usually affected, either simultaneously or with a short interval. It is often seen accompanying impetigo, scarlatina, measles or small pox, but there are two types which often present characteristics that differ with the bacterial agent.

The first of these is due to the Koch-Weeks bacillus. It occurs mostly in young people in an epidemic form; it is usually more severe in adults. Numerous ecchymoses occur in the bulbar conjunctiva, hence the common name "pink" eye.

The second is due to the pneumococcus. A characteristic of this form is an œdema along the margin of the upper lid and the lower fornix, spreading on to the bulbar conjunctiva, which gives the appearance of a gelatinous chemosis without any more than a rose coloured hyperæmia. It generally lasts only eight to ten days and subsides so quickly that it can be termed a decline by crisis. It is sometimes seen in pneumonia or bronchopneumonia and often occurs as the result of an infected tear sac.

Chronic catarrhal conjunctivitis is usually a very obstinate condition occurring in adults and old people when it is not unusual to find a rough or velvety palpebral conjunctiva and ectropion of the lower lid with epiphora. There is, however, a definite clinical variety that is important because it yields to certain treatment. It is commonly known as "angular" conjunctivitis and may be seen in a subacute or more often a chronic form, the exciting cause being the diplobacillus of Morax-Axenfeld. The congestion is chiefly confined to the margins of the lids, especially the lower, the canthi and the caruncles, hence the term "angular."

Purulent Conjunctivitis.

Purulent conjunctivitis is a very dangerous condition, having in the past been one of the commonest causes of blindness, seen mostly as gonorrhœal or streptococcal *ophthalmia neonatorum*.

When I was at Moorfields, all infants with purulent ophthalmia were sent up to the laboratory for bacteriological investigation and it was found that in more than half the cases the staphylococcus and streptococcus were isolated, while in only about 30% of the cases could the gonococcus be detected. The characteristics of the condition are red lids, which become intensely swollen and hot in a few hours, preventing the patient and often the physician from separating the lids. The reddish serous discharge soon becomes profusely purulent, the eye very tender, the lymphatic gland in front of the ear swollen and the patient feverish. After a lapse of one to three days the other eye begins the same course of events unless it has been successfully protected from infection, as can occasionally be done in an adult.

Membranous Conjunctivitis.

In addition to the usual signs and symptoms found in catarrhal conjunctivitis these cases are characterized by a fibrinous exudate on the surface or in the substance of the conjunctiva. The condition is not pathognomonic, but is very suggestive of the presence of the Klebs-Löffler bacillus, and this organism should be excluded as soon as possible.

Other organisms which cause a membranous exudate, are the pneumococcus, streptococcus and staphylococcus. In a typical case of diphtheritic conjunctivitis the membranous exudate is confined to the palpebral conjunctiva and there is great constitutional disturbance with swelling of the preauricular and submaxillary glands.

Phlyctenular Conjunctivitis.

If phlyctenular conjunctivitis is really an infection of the conjunctiva, then the organism has yet to be isolated. The tubercle bacillus and staphylococcus have been blamed and occasionally isolated from the phlyctens, but their guilt has yet to be proved. It is so often found in strumous and improperly fed children who are shut away or live where there is a relative absence of sunlight, that it is now regarded as a deficiency disease in which ultraviolet radiation and proper attention to diet have in England been found almost a specific. This probably accounts for its extreme rarity in Australia and consequently there is no need for further mention of this condition than to say that the phlyctens are usually found in the limbus with intense conjunctival injection, and one of its most characteristic features is the intense photophobia to which it gives rise.

Trachoma.

Trachoma, which is fortunately becoming very much less prevalent in Australia, is a chronic inflammatory disease of the conjunctiva which originates by infection. The nature of the organism concerned, however, has so far not been determined. Many organisms have in the past been isolated, but later found to be the result of mixed infections.

Noguchi in 1927 isolated a Gram-negative diphtheroid organism from the lids of Mexican Indians apparently infected with trachoma, but all efforts to transfer the disease by inoculation to monkeys have failed, and it has been pointed out by Mayou that the pathology of the disease in Mexican Indians is very different from that found elsewhere. We therefore have to depend mainly on clinical manifestations to form our diagnosis, the pathologist occasionally assisting in doubtful cases by demonstrating the presence of cell inclusions.

It is a disease that is influenced by racial, climatic and social conditions, characterized by the development of translucent greyish granulations, so-called "sago grain" bodies, mostly in the upper lid near the upper limit of the tarsus and in the loose reflected tissue of the upper fornix. Papillary formations still further enhance the unevenness of the conjunctival surface. This so-called papillary stage of the disease is followed at some time by the development of fibrous cicatricial tissue, the contraction of which is responsible for the mutilating complications which ensue. The cornea is so frequently involved by pannus, a superficial vascularization of the cornea almost invariably commencing in the upper part of the cornea, that it has come to be regarded as a characteristic of the disease and it is because of this and perhaps some small corneal infiltrations that ptosis and photophobia are so frequently seen in these patients. Victims of trachoma often tolerate the disease to a remarkable degree and frequently do not come up until they have a mixed or superimposed infection giving rise to the so-called acute type of case. There is usually no difficulty in making a diagnosis in the later stages of trachoma, when pannus, scarring and a gelatinous conjunctiva are present, but occasionally patients come up in the initial stages, when diagnosis is most difficult. It is important to elicit the place of abode or whether there is a possibility of contact. A thorough and careful examination of the whole conjunctival sac must be made in order to avoid missing the

condition or making a wrong diagnosis, because the formation of granulations is for a long time confined to the retro-tarsal folds and this, together with some hypertrophy of the conjunctiva, will produce a slight ptosis by which symptom alone a careful observer will be able to make sure of his diagnosis.

Differential Diagnosis of Trachoma.

In follicular conjunctivitis, which is really a formation of follicles in catarrhal conjunctivitis, the follicles are nearly always confined to the lower lids, are less numerous, smaller, more uniform in size and regular in arrangement than in trachoma. They also have a more transparent appearance, with a well defined outline appearing to be on the conjunctiva rather than in it, and seldom occur on the tarsal conjunctiva. Trachoma follicles, on the other hand, are coarse, irregular, greyish, ill defined and frequently confluent, lying in the deeper tissues, always affecting the upper lid.

In spring catarrh, a chronic disease of the tarsal conjunctiva of the upper lid, which becomes covered with hard, flattened, pinkish elevations arranged close together, giving rise to the so-called "pavement" granulations, the fornices are never involved and the conjunctival secretion contains numerous eosinophile cells.

Monocular Conjunctivitis.

My reason for honouring the unfortunate term monocular conjunctivitis with a special reference is the fact that it is the cause of more mistakes than anything so far discussed in this paper. I do not wish to convey the impression that the other types of conjunctivitis mentioned above always involve both eyes simultaneously; on the contrary, it is more usual in the acuter types for a varying interval to occur between the involvement of the two eyes. Always be on guard when confronted with what appears to be a monocular conjunctivitis, because there is really only one type, and that a rare one, which can be truly said to attack only one eye; this is Parinaud's conjunctivitis. It is a well defined subacute condition ushered in with chills and malaise associated with painful enlargement of the preauricular gland. Subjective eye symptoms are slight, with swelling of the upper lid, slight chemosis and reddish granulations on the tarsal conjunctiva and fornices.

I can perhaps best illustrate this important subject by referring in a group to some of the patients who have been sent to me as sufferers from monocular conjunctivitis resisting all treatment. One was a farmer with a piece of chaff embedded high up in the upper fornix. A lady had a piece of leaf in the same position. Neither of these gave a history of such a possibility. A barber had a piece of hair in the upper canaliculus, the end of which was protruding from the punctum and mechanically irritating the bulbar conjunctiva on that side. Others were patients with chronic dacryocystitis, inturned eyelashes, episcleritis and corneal foreign body.

I have seen so many mistakes made with superficial punctate keratitis that I should like to point out here that in addition to the usual ciliary injection seen in these cases the bulbar and palpebral conjunctiva is more or less injected as well, and there is a good deal of lachrymation, but no mucoid or purulent discharge. It is often associated with an infection of the upper respiratory tract. The punctate spots of infiltration in the periphery of the cornea are so small in many cases as to escape detection unless a drop of fluorescin is instilled, then well washed out, and the cornea examined, preferably by the slit lamp or failing that, good focal illumination with a binocular loupe.

Then last, but by no means least, come our old friends iritis and glaucoma. I do not intend to go into a description of the diagnosis of these conditions, as they have already been discussed in separate articles in this series.

Summary.

It will be quite sufficient for me to summarize this subject by pointing out that most mistakes are the result of an incomplete examination. This can best be avoided by getting into the habit of a routine examination of all the structures concerned, irrespective of what the patient complains. It takes so little time to look thoroughly in this order at the skin of the lids, lashes, lid margins, puncta and then to squeeze over the site of the sac, to evert the lids thoroughly and to examine the fornices, palpebral conjunctiva and then to pass on to the bulbar conjunctiva, noting the presence of any injection from which ciliary and episcleral injection should be distinguished; to note: the cornea, its transparency and surface condition, as illustrated by the light reflex; the tension of the eye; the anterior chamber; its depth and nature of its contents; the iris, its colour pattern, activity and size of the pupils. The whole thing is a matter of a few moments' concentrated observation in a good light.

If this paper, which is all the more difficult because of the apparently simple nature of the subject, has done nothing more than convert a few general practitioners to the above systematic routine, then I shall feel that it has not been in vain.

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British Medical Association News.

SCIENTIFIC.

A MEETING OF THE NEW SOUTH WALES BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the School of Public Health and Tropical Medicine, University of Sydney, on April 9, 1931.

The visitors were conducted through the buildings by Professor Harvey Sutton and other members of the staff. Particular attention was paid to the library and the animal house.

Demonstration of Specimens.

DR. G. A. M. HEYDON demonstrated the following specimens:

1. Infective hookworm larvæ extending themselves into the air singly and in groups from prominent particles on the surface of moist earth.
2. Infective hookworm larvæ in a von Esmarch rolled tube of agar to demonstrate their thermotropism. When a finger is placed on the outside of the tube the larvæ swarm beneath it.
3. Kitten showing rash on skin due to penetration of hookworm larvæ two days previously.
4. Antiformin-sugar flotation method for the diagnosis of intestinal worm infestations. Hookworm and ascaris eggs were shown.
5. Apparatus designed at the School of Public Health and Tropical Medicine for the isolation of larvæ of parasitic worms from earth, cultures and organs or tissues.
6. The larvæ of the dog and cat hookworms (*Ancylostoma braziliense* and *Ancylostoma caninum*) which cause creeping eruption in North Australia, popularly called sandworm. Photographs of patients were shown.
7. Living microfilariæ in blood.
8. Section of a mosquito, *Anopheles amictus*, showing larvæ of *Filaria bancrofti* in the head and proboscis; north Queensland.
9. Salivary gland of *Anopheles punctulatus* containing malarial sporozoites, from Rabaul.
10. Section of brain from a case of cerebral malaria showing masses of plasmodia in the vessels.
11. Sections of liver and kidney from a case of carbon tetrachloride poisoning.

MR. F. H. TAYLOR showed a collection of flies of importance in public health work, comprising specimens of *Anopheles*, *Culex*, *Stegomyia*, *Musca*, *Stomoxys*, and various blowflies, the red-back spider, *Latrodectus haseltii*, the trapdoor spider, *Atrax robustus*, the scrub tick of eastern Australia, *Ixodes holocyclus*, the kangaroo tick, *Ornithodorus gurneyi*.

Mr. Taylor showed photographic enlargements of: (1) the life history of the house mosquito, *Culex fatigans*;

(ii) a mosquito feeding on the hand; (iii) the house fly feeding on a drop of honey; (iv) a March fly in the act of biting. (The above four photographs were from negatives kindly lent by Dr. A. J. Nicholson.)

Mr. Taylor also showed enlargements of photomicrographs of: (i) the egg of the head louse, showing two stages of development of the embryo within the egg; (ii) the head of a sand fly; (iii) a wingless fly parasitic on flying foxes.

Elevation of Bodily Temperature in the Tropics.

DR. A. H. BALDWIN spoke briefly on the causes that might underlie a rise in bodily temperature in the tropics. He first mentioned physiological rises in temperature and the differences noted between oral and rectal temperatures, and the question of acclimatization was touched on. Attention was drawn to the different behaviour of some diseases in the tropics to that which they exhibited in more temperate latitudes.

The speaker then briefly reviewed some of the pathological conditions giving rise to fever in the tropics of Australia, including lead poisoning in children, X disease, typhoid infection with atypical strains, endemic typhus, *Bacillus pyocyaneus* infections, dengue, Mossman fever, Sarina fever, filarial and hookworm infections, and raised the question whether Mossman fever might not be a leptospirosis. He concluded by pointing out that it was a common mistake to imagine the tropical practitioner in Australia was constantly dealing with strange fevers and tropical diseases; his work in reality consisted in dealing with just those diseases met with in temperate zones, perhaps modified to some extent by a tropical climate, together with a very small fraction of true tropical disease.

Laboratory Animals.

DR. W. C. SAWERS read a paper in which he discussed the provision of animals for experimental purposes. He pointed out that animals were essential for demonstration in teaching and for research. Mice, rats, guinea-pigs, rabbits, monkeys, dogs and possibly cats, sheep and even birds were necessary. In large laboratories provision would have to be made for horses, sheep and goats. Accommodation had to be provided for both uninfected and infected animals. The need for guarding against cross infection had to be borne in mind. Dr. Sawers described the method of storage, the construction of a *post mortem* room, the construction and arrangement of cages, the need for an isolation block, an incinerator and a disinfectant tank. After discussing each of these items in detail, Dr. Sawers referred to the source of animal supply and to the location of animal accommodation. He showed that in the construction of the animal house at the School of Public Health and Tropical Medicine an attempt had been made to adapt the essentials to the needs of the several departments of the school.

The Distribution of Stegomyia Argenteus in Australia.

MR. F. H. TAYLOR discussed the distribution of *Stegomyia argenteus* in Australia. He said that this mosquito had been in Queensland for at least fifty years, since specimens were known that were taken at Cunnamulla, Western Queensland, in 1881. Cunnamulla lay some 600 miles from Brisbane in a south-westerly direction. It must have taken several months at least for the spread either in the egg, larval or adult stage of this mosquito from the coast. It was well established over the entire State of Queensland, at Darwin in North Australia, and at Broome and Derby in the north-west of Western Australia.

The northern rivers of New South Wales, as far as Lismore at least, had been infested for a long time, the mosquito having gradually spread south until it was found at Newcastle in 1911. Since that date, or perhaps during its progress southward, this mosquito had gradually occupied the north-west of New South Wales, so that by 1925 it was found occupying the territory north of a line drawn between Newcastle and Bourke.

During January to February, 1931, a survey was made of the towns on the railway line between Sydney and Newcastle, when the habitat furthest south was established at Brooklyn (Hawkesbury River).

Schools of Hygiene in Other Lands.

PROFESSOR HARVEY SUTTON, in a lantern lecture on schools of hygiene in other lands, discussed their activities and the methods used in Canada, the United States of America, England, Poland and Jugo-Slavia. The lecture also included similar schools or teaching departments in other universities dealing with tropical medicine and hygiene and their part in the medical curriculum.

These schools, which existed largely because of munificent subsidies from the Rockefeller Foundation, at present exist at Toronto, Baltimore (Johns Hopkins), Boston (Harvard), London, Warsaw and Zagreb, and new schools would appear shortly at Budapest, Prague, Madrid and Athens, while that of Calcutta was already flourishing. Tropical schools at Liverpool, Hamburg and Paris (Pasteur Institute) were also visited.

The main function was the training of health personnel, especially medical officers of health and medical students, and also the carrying out of investigations into matters of health importance. Such research was undertaken not only in order to advance knowledge, but also as the basis of successful teaching.

Everywhere it was agreed that a close nexus of schools of health with the university was essential, and further that health education should extend to non-medical health personnel and to the public in general.

Of equal importance with the post-graduate instruction for diplomas was the work done with the medical student by lectures and field work in public health and preventive medicine. While every teacher in the medical curriculum should emphasize the preventive idea, the school of hygiene was regarded as amplifying the experience of the student and illustrating the instruction given by the professor of preventive medicine.

Among the special features encountered by Professor Sutton were thorough systems of health supervision of students at Berkeley, Toronto and McGill Universities, the advanced scientific courses of instruction at Johns Hopkins, the Surgeon-General's Library, Washington, and the Welch Library at Baltimore, the course for public health nurses at Toronto, the training of social workers at Boston, the remarkable display at the Wellcome Museums on the History of Medicine and on Medical Science, London.

The great London School was opened in July, 1929, and led the world in post-graduate training of medical officers of health. It was established with the help of a gift of £400,000 from the Rockefeller Foundation and is maintained by the British Government.

The most striking experience of all was the visit to Zagreb (Agram) the central school of hygiene for Jugo-Slavia, the country of the Serbs, Croats and Slovenes. Since the war a modern city had rapidly developed within a mediaeval town.

A large, well equipped and up-to-date school of hygiene, which housed the University Institute of Hygiene and a serum department, controlled an excellent health nursing school on the Toronto pattern, and a hospital for infectious diseases. The school made its own cinema films, a valuable means of instruction for a largely illiterate adult population, and printed its own books. Two most unusual and interesting activities were here in full working order. The year after medical graduation was a probation year, which was allotted to hospital work, half of which was clinical (medical, surgical and obstetric) and half was devoted to hospital and field work in health, attending various clinics, dispensaries, welfare centres, laboratories *et cetera*, dealing with tuberculosis, syphilis, trachoma, welfare work, school medical inspection, infectious diseases. From this the graduate passed either into the health service or into private practice.

The second activity was that of the "Peasants" University. The village life of the country around was most primitive (wooden ploughs, "shadoofs" for wells), while mediaeval conditions of housing and habits made the task of health improvement most difficult. Demonstration centres with a health nurse in charge established in these villages were doing much to improve matters, especially the unusually high death rate among mothers and children.

Finally, allusion was made to the widespread activities of the Health Section of the League of Nations and also to the International Labour Office (Industrial Hygiene).

The School of Public Health and Tropical Medicine was now recognized by the League of Nations and by the British Colonial Office as a training ground for medical health personnel and as a centre for investigation of Oceania and its tropical problems.

Post-Graduate Work.

ANNUAL REFRESHER COURSE IN MELBOURNE.

THE Melbourne Permanent Committee for Post-Graduate Work announces that the annual refresher course will be held from August 17 to 28, 1931. The fee for the course is three guineas. In order to facilitate the work of the Committee, it is requested that entries for the course be forwarded before August 1 and that visitors will give a Melbourne address. Later entries will, of course, be received. Arrangements have been made whereby a limited amount of accommodation will be available at the Melbourne and Alfred Hospitals for those attending the course at an additional fee of three guineas per week to cover board and lodging. Applications should be addressed to the Honorary Secretary of the Committee, 12, Collins Street, Melbourne.

Attention is again drawn to the special series of lectures on bacteriology and immunology to be delivered by Dr. F. M. Burnet during the progress of the course. These lectures are entirely separate from the course; the fee for the lectures is two guineas. The syllabus was published in THE MEDICAL JOURNAL OF AUSTRALIA of April 11, 1931, at page 457.

The syllabus for the refresher course is as follows:

Monday, August 17, 1931.

9 to 9.30 a.m.—Registration at Post-Graduate Office, Melbourne Hospital.

9.30 to 11 a.m., at the Melbourne Hospital.—Mr. A. E. Coates: Clinical demonstration of the treatment of acute appendicitis and its complications.

11.15 a.m. to 12.45 p.m., at the Melbourne Hospital.—Dr. F. Blois Lawton: Demonstration of cases of pulmonary disease.

2.15 to 3.30 p.m., at the Melbourne Hospital.—Dr. H. F. Maudsley: "Early Mental Disease, with Special Reference to Prognosis."

3.30 to 5 p.m., at the Melbourne Hospital: "Clinical Pathology, with Special Reference to Methods Suitable for Use in Practice," arranged by Dr. Lucy Bryce.

8.30 p.m., at the Walter and Eliza Hall Institute (Melbourne Hospital).—Dr. F. M. Burnet: Lecture I, "The Basis of Immunology."

Tuesday, August 18, 1931.

9.30 to 11 a.m., at Saint Vincent's Hospital.—Mr. H. B. Devine: "Diagnosis and Management of Lesions of the Left Iliac Fossa."

11.15 a.m. to 12.45 p.m., at Saint Vincent's Hospital.—Dr. W. J. Newing: "Treatment of Hyperextension. Induction of Artificial Pneumothorax."

2.15 to 3.30 p.m., at the Children's Hospital.—Dr. Stewart Ferguson: "Diet and Diarrhœa in Infancy."

3.30 to 5 p.m., at the Children's Hospital.—Dr. H. Douglas Stephens: "Abdominal Conditions in Children."

8.30 p.m., at the Walter and Eliza Hall Institute.—Dr. F. M. Burnet: Lecture II, "Immunological Aspects of Bacterial Infections."

Wednesday, August 19, 1931.

9.30 to 11 a.m., at the Women's Hospital.—Professor Marshall Allan: "Labour in the Elderly Primipara."

11.15 a.m. to 12.45 p.m., at the Women's Hospital.—Dr. Edward R. White: "Some Common Diseases in Gynæcology."

2.15 to 3.30 p.m., at Saint Vincent's Hospital.—Dr. Eccles MacKay: "Leucorrhœa, Vaginitis, Cervicitis."

3.30 to 5 p.m., at Saint Vincent's Hospital.—Dr. John O'Sullivan: Demonstration of gastro-intestinal and other radiographs.

8.15 p.m., at the Alfred Hospital.—British Medical Association Victorian Branch clinical meeting.

Thursday, August 20, 1931.

9.30 to 11 a.m., at the Alfred Hospital.—Dr. J. P. Major: "Some Blood Diseases and Their Treatment."

11.15 a.m. to 12.45 p.m., at the Alfred Hospital.—Mr. Hugh Trumble: "Plasters."

2.30 to 5 p.m., at the Infectious Diseases Hospital, Fairfield.—Dr. F. V. Scholes and Staff: Demonstration of infectious diseases cases.

Friday, August 21, 1931.

9.30 to 11 a.m., at the Melbourne Hospital.—Mr. Allan Hailes: "Acute Intestinal Obstruction."

11.15 a.m. to 12.45 p.m., at the Melbourne Hospital.—Dr. Hume Turnbull: "Nodular Goître."

2.15 to 3.30 p.m., at the Alfred Hospital.—Dr. S. W. Shields: Clinical demonstration in dermatology.

3.30 to 5 p.m., at the Alfred Hospital (The Baker Medical Research Institute): Series of demonstrations.

8.30 p.m., at the Walter and Eliza Hall Institute.—Dr. F. M. Burnet: Lecture III, "Immunological Aspects of Bacterial Infections" (continued).

Saturday, August 22, 1931.

9.30 to 11 a.m., at the Melbourne Hospital.—Mr. Alan Newton: "Diseases of Biliary Tract."

Monday, August 24, 1931.

9.30 to 11 a.m., at the Melbourne Hospital, Dr. W. W. S. Johnston: "Some Aspects of Nephritis."

11.15 a.m. to 12.45 p.m., at the Melbourne Hospital.—Mr. B. T. Zwar: "Advances in the Surgery of Pleuritic and Lung Conditions."

2.15 to 3.30 p.m., at the Melbourne Hospital.—Mr. G. C. Scantlebury: "Ear, Nose and Throat Conditions."

3.30 to 5 p.m., at the Melbourne Hospital.—Dr. John Kelly: "Diagnosis and Treatment of Skin Diseases, with a Series of Cases."

8.30 p.m., at the Walter and Eliza Hall Institute.—Dr. F. M. Burnet: Lecture IV., "Modern Work on Epidemiology."

Tuesday, August 25, 1931.

9.30 to 11 a.m., at the Alfred Hospital.—Dr. J. F. Chambers: "Endocrine and Allied Disturbances."

11.15 a.m. to 12.45 p.m., at the Alfred Hospital.—Mr. Alfred Trinca: "Sepsis of the Hand."

2.30 to 5 p.m., at the Eye and Ear Hospital.—Members of the Clinics of Dr. J. Rudall, Dr. Mark Gardner and Dr. J. O'Brien: Demonstration of methods of examination, minor operations, diagnosis and treatment of common eye diseases.

Wednesday, August 26, 1931.

9.30 to 11 a.m., at the Women's Hospital.—Dr. Arthur Wilson: "Indications for Induction of Premature Labour."

11.15 a.m. to 12.45 p.m., at the Women's Hospital.—Dr. John Green: "Difficult Vertex Cases."

2.15 to 5 p.m., at the University of Melbourne, Anatomy Department.—Professor Wood Jones and Staff: Demonstrations in Surgical Anatomy.

8.30 p.m., at the Walter and Eliza Hall Institute.—Dr. F. M. Burnet: Lecture V, "The Filterable Viruses."

Thursday, August 27, 1931.

9.30 to 11 a.m., at Saint Vincent's Hospital.—Dr. J. G. Hayden: "Recent Advances in the Diagnosis and Treatment of Cardiac Disease."

11.15 a.m. to 12.45 p.m., at Saint Vincent's Hospital.—Mr. Gordon Shaw: Clinical demonstration of diseases and injuries of the wrist.

2.15 to 3.30 p.m., at the Children's Hospital.—Dr. D. M. Embelton: "Bronchiectasis, Pulmonary Abscess and Damaged Lung in Children."
3.30 to 5 p.m., at the Children's Hospital.—Dr. Rupert Downes: "Head Injuries and Other Conditions in Children."

Friday, August 28, 1931.

9.30 to 11 a.m., at the Melbourne Hospital.—Mr. Victor Hurley: "Cases Illustrating Pre- and Post-Operative Treatment in Diseases of the Thyreoid and Prostate Glands and in Surgical Complications of Diabetes."
11.15 a.m. to 12.45 p.m., at the Melbourne Hospital.—Dr. S. V. Sewell: "Some Causes of Headache."
2.30 to 5 p.m., at the Central Tuberculosis Bureau.—Dr. J. Bell Ferguson: "Some Modern Methods in the Treatment of Pulmonary Tuberculosis."
Dr. H. M. James: Demonstration of radiographs.
8.30 p.m., at the Walter and Eliza Hall Institute.—Dr. F. M. Burnet: Lecture VI, "The Modern Theory of Anaphylaxis."

Demonstrations at the Melbourne Hospital will include the following:

Monday, August 17, 3.30 *to* 5 *p.m.*

Dr. Lucy Bryce and Dr. H. Gardner: Clinical bacteriology and pathology.
Miss B. Splatt, B.Sc.: Biochemistry.
Miss C. Maudsley, B.Sc.: Electrocardiograph and estimation of basal metabolic rate.

The demonstration at the Alfred Hospital will be as follows:

August 21, 1931, 3.30 *to* 5 *p.m.*

(1) Diagnostic errors in everyday cases.—Dr. Willis.
(2) Intermittent glycosuria as a cause of *pruritus vulvæ*.—Miss M. Long, M.Sc.
(3) The prevention and treatment of diabetic coma.—Dr. Downie.
(4) A simple and rapid serological test for syphilis.—Miss Ashworth, B.Sc.
(5) Practical points in the diagnosis of pernicious anæmia.—Dr. Corkill and Dr. Jones.

Obituary.

RICHARD PERKINS.

WE regret to announce the death of Dr. Richard Perkins which occurred at Manly, New South Wales, on June 15, 1931.

Diary for the Month.

JULY 14.—New South Wales Branch, B.M.A.: Ethics Committee.
JULY 21.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JULY 22.—Victorian Branch, B.M.A.: Council.
JULY 24.—Queensland Branch, B.M.A.: Council.
JULY 28.—New South Wales Branch, B.M.A.: Medical Politics Committee.
JULY 30.—South Australian Branch, B.M.A.: Branch.
JULY 30.—New South Wales Branch, B.M.A.: Branch.
AUG. 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
AUG. 5.—Victorian Branch, B.M.A.: Branch.
AUG. 6.—South Australian Branch, B.M.A.: Council.
AUG. 7.—Queensland Branch, B.M.A.: Branch.
AUG. 11.—New South Wales Branch, B.M.A.: Ethics Committee.

Medical Appointments Vacant, etc.

FOR announcements of medical appointments vacant, assistants, *locum tenentes*, sought, etc., see "Advertiser," page xiv.

PERTH HOSPITAL, PERTH, WESTERN AUSTRALIA: Medical Superintendent.
ROYAL AIR FORCE, MEDICAL BRANCH: Medical Officers.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members desiring to accept appointment in ANY COUNTRY HOSPITAL, are advised to submit a copy of their agreement to the Council before signing, in their own interests. Brisbane Associated Friendly Societies' Medical Institute. Mount Isa Hospital. Mount Isa Mines. Toowoomba Associated Friendly Societies' Medical Institute.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

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